Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 3003–3008

TETRAHEDRON

Synthesis and biological activity of α,β,γ,δ-unsaturated aldehydes from diatoms

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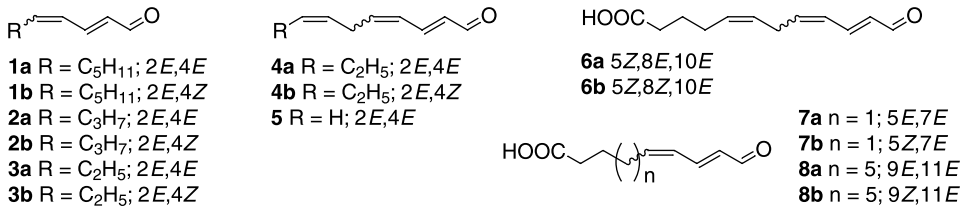
Received 16 January 2003; revised 10 March 2003; accepted 13 March 2003

Abstract—α,β,γ,δ-Unsaturated aldehydes have gained increasing attention since 2,4-decadienal and 2,4,7-decatrienal were isolated from the diatom *Thalassiosira rotula* and characterized as cell antiproliferative metabolites. Structurally related α,β,γ,δ-unsaturated aldehydes were found in this alga as well as in other diatom species. We present a short and universal synthesis of this compound class along with a structure–activity study of the potential to inhibit sea urchin egg cleavage. Pd^0- or Co^{II}-mediated cross coupling of 5-iodo-penta-2,4-dienal with organo-zincates allows the fast and flexible synthesis of numerous aldehydes from this universal precursor. The stereochemistry of the double bond system of the precursor was preserved during the coupling. Bioassays showed that the polarity of the side chain is important for antiproliferative activity with 2,4-decadienal as the most active compound tested compared to the shorter-chain aliphatic homologues and to ω-oxo acids with conjugated double systems. In contrast, the double bond geometry has no influence on biological activity. The α,β-unsaturated 2*E*-decenal was also highly active, while activity diminished in the case of saturated aldehydes of similar chain length. 1-Decanol, 2-decanone and decanoic acid were not active.

1. Introduction

Diatoms are among the most abundant algae in phytoplankton and contribute significantly to global carbon fixation. These unicellular algae are also an important basis of the marine food chain. Despite their significance, little is known about their chemical defence. Recently, it was reported that 2*E*,4*E*/*Z*-decadienal (**1ab**), and 2*E*,4*E*/*Z*,7*Z*-decatrienal (**4ab**) from the marine diatom *Thalassiosira rotula* act antiproliferatively against herbivorous copepods.[1] These aldehydes are derived from the lipoxygenase/hydroperoxid lyase dependent degradation of arachidonic or eicosapentaenoic acid that takes place within seconds after wounding of the diatom cells.[2–4] If administered to copepod eggs 2*E*,4*E*/*Z*-decadienal (**1ab**), and 2*E*,4*E*/*Z*,7*Z*-decatrienal (**4ab**) inhibit cell cleavage with similar thresholds of ca. 1 mg L^{-1}.[1] Previous studies with sea urchin eggs found comparable effects and threshold concentrations.[5] It was concluded that these aldehydes in the copepod maternal diet reduce the viability of the offspring, thus acting as a wound-activated chemical defence. Besides 2*E*,4*E*/*Z*-decadienal (**1ab**), and 2*E*,4*E*/*Z*,7*Z*-decatrienal (**4ab**), other α,β,γ,δ-unsaturated aldehydes have been identified after cell disruption of diatoms (Scheme 1).[2–8]

T. rotula releases in addition the shorter-chain unsaturated aldehydes 2*E*,4*E*/*Z*-heptadienal (**3ab**), 2*E*,4*E*/*Z*-octadienal (**2ab**) and 2*E*,4*E*,7-octatrienal (**5**) as well as elevated amounts of saturated aldehydes.[5,7] *Skeletonema costatum* and *S. pseudocostatum* release predominantly 2*E*,4*E*/*Z*-heptadienal (**3ab**) and 2*E*,4*E*/*Z*-octadienal (**2ab**),[5,8]



Scheme 1. α,β,γ,δ-Unsaturated alehydes from diatoms.

Keywords: aldehydes; 2,4-dienals; synthesis; cell division; diatoms; Michael-acceptor; bioassays.
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0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00382-X

while the fresh-water diatoms *Gomphonema parvulum* and *Asterionella formosa* produce 9-oxo-nona-5*Z*,7*E*-dienoic acid (**7b**) and 12-oxo-dodeca-5*Z*,8*Z*,10*E*-trienoic acid (**6a**), respectively.[2,3] Despite the potential role of these aldehydes in the chemical defence of diatoms, no detailed structure-activity investigation has been reported and the few bioassays[1,5,8] rely on purified material or crude commercially available mixtures of 2*E*,4*E*-decadienal (**1a**) and 2*E*,4*Z*-decadienal (**1b**).

Here we present a short synthesis of isomerically pure α,β,γ,δ-unsaturated aldehydes, a compound class also known as inhibitors of embryonic development of marine invertebrates,[9] as cytotoxic agents against human erythrocytes,[10] as DNA-alkylating agents,[11] and, fused to phospholipids, as potential signalling molecules in mammals.[12] The biological activity of the aldehydes found in diatoms was characterized by their potential to inhibit cell division in sea urchin eggs, and the activity was compared with other short chain fatty acids, ketones, and aldehydes.

2. Results and discussion

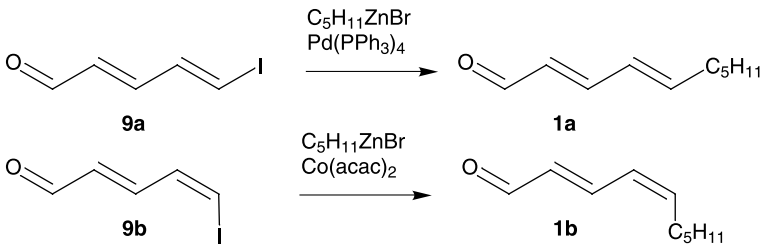
2.1. Synthesis of α,β,γ,δ-unsaturated aldehydes

The importance of α,β,γ,δ-unsaturated aldehydes as biologically active molecules as well as building blocks for polyenes resulted in numerous synthesis of these compounds. These often rely on deprotection and oxidation of alcohols in the final reaction steps,[2] generate the unsaturated aldehydes by electrocyclic ring opening of cyclobutenes[13] or use Wittig-procedures in multistep-approaches.[12] Other sequences do not provide access to both isomers of the double bond at C4-position[14] or allow only the generation of the 2*Z*-isomers.[15] Our aim was to synthesize the set of α,β,γ,δ-unsaturated aldehydes found in diatoms with a minimum number of manipulations after completing the aliphatic or carboxylic chains of the target molecules. Using 5-iodo-penta-2*E*,4*E*-dienal (**9a**) or 5-iodo-penta-2*E*,4*Z*-dienal (**9b**) as key-intermediates, we could exploit the pre-formed α,β,γ,δ-unsaturated aldehyde for coupling reactions and finish the aldehydes with both isomers of the γ,δ-double bond in one reaction step. The coupling protocols proved to be tolerant to aliphatic esters, allowing build-up of unsaturated ω-oxo-acids from the same precursors in two steps. 5-Iodo-penta-2*E*,4*E*/*Z*-dienal (**9ab**) thus serves as an universal key-intermediate that allows the flexible generation of α,β,γ,δ-unsaturated aldehydes.

The iodide **9ab** could be generated on a multigram scale in two steps following known procedures as a 55:45 mixture of 2*E*,4*E*- and 2*E*,4*Z*-isomers.[16,17] This mixture was purified by flash chromatography on florisil using a binary solvent of petrol-ether: THF (99:1) as mobile phase. Both isomers can be separated and stored for several months at −20°C in a benzene matrix. The coupling reactions of **9a** with organozincates or dialkyl zinc reagents proceeded smoothly, retaining the configuration of the double bonds using $Pd(PPh_3)_4$ as a catalyst (Scheme 2, Table 1). In contrast, application of this protocol to the coupling of **9b** yielded primarily the more stable undesired 4*E*-isomers. The isomerization during the coupling reaction can be exploited to generate 2*E*,4*E*-dienals from isomeric mixture of the iodide **9ab** without prior separation. In contrast to previously reported stereoselective cross couplings with Pd^0 and vinylic iodides[18] that rely on a kinetic discrimination of the educts, here the entire pool of 4*E*- and 4*Z*-isomers of the iodide are transformed predominantly to 2*E*,4*E*-dienals.

Using cobalt-catalyzed alkenylation of zinc organometallics,[19] this isomerization could be prevented and the isomeric purity of **9b** was conserved during the coupling (Scheme 2, Table 1).

This $Co(acac)_2$-mediated coupling could also be applied to



Scheme 2. Transition-metal mediated coupling of vinylic iodides.

Table 1. Transition metal-mediated preparation of α,β,γ,δ-unsaturated aldehydes

Metal species	Catalyst	Reaction time (min)	*T* (°C)	Yield
$C_5H_{11}ZnBr$	$Pd(PPh_3)_4$	20	−78	**1a** 79% (4*E*/*Z*>95/5)[a]
$C_5H_{11}ZnBr$	$Co(acac)_2$	15	−30–0	**1b** 81% (4*E*/*Z*<5/95)[b]
C_3H_7ZnBr	$Co(acac)_2$	30	−30–0	**2a**,**b** 47% (4*E*/*Z*=55/45)[c]
C_2H_5ZnBr	$Co(acac)_2$	30	−30–0	**3a**,**b** 49% (4*E*/*Z*=55/45)[c]
$(EtOOCC_3H_6)_2Zn$	$Co(acac)_2$	30	−30–0	**7a**,**b** 49% (5*E*/*Z*=55/45)[c]
$(MeOOCC_7H_{14})_2Zn$	$Co(acac)_2$	30	−30–0	**8a**,**b** 53% (9*E*/*Z*=55/45)[c]

[a] From pure 2*E*,4*E*-iodide **9a**.
[b] From pure 2*E*,4*Z*-iodide **9b**.
[c] From the 2*E*,4*E*/*Z*-mixture of **9ab**.

2*E*,4*E*/*Z*-mixtures of the vinylic iodide **9ab** without loss of the configuration of the double bonds giving access to mixtures of 4*E* and 4*Z* isomers. Since the isomers of α,β,γ,δ-unsaturated aldehydes are easily separable by column chromatography on SiO_2, we simplified the preparation of a multitude of isomeric dienals by reacting the mixture of 2*E*,4*E*/*Z*-vinylic iodides **9ab** with the respective alkylzincates and separating the resulting aliphatic aldehydes.

To generate the ω-oxo-acids **7ab** and **8ab**, we used 4-iodo-butanoic acid ethyl ester or 8-iodo-octanoic acid methyl ester which had been transformed to the di-alkanoic acid ester-zinc-compounds using diethylzinc.[20] These were coupled with the iodide **9ab** using $Co(acac)_2$ and the purified products were saponified with porcine liver esterase (PLE).[21] After extraction the free acids could be directly used for biological testing.

2.2. Biological activity

To test for activity of the 2,4-dienals, as well as of other aldehydes from diatoms, we monitored the inhibition of cell division in synchronized sea urchin eggs (*Sphaerechinus granularis*) incubated with test compounds added to seawater. As a control, the threshold concentrations and IC_{50} for the inhibition of the first cell cleavage by a commercially available mixture of 2,4-decadienal isomers and by taxol were compared with those from previous experiments[5] and proved to be highly reproducible.

To test for the influence of the isomeric composition and of the length of the aliphatic chains, the activity of the alkyl-substituted 2,4-dienals **1a**,**b**, **2a**,**b**, and **3a**,**b** was tested (Fig. 1).

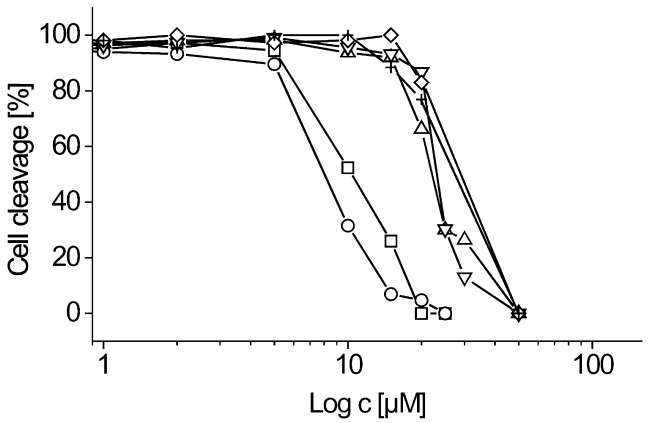


Figure 1. Inhibition of the first cell cleavage in sea urchin eggs by 2*E*,4*E*-decadienal (**1a**) (○), 2*E*,4*Z*-decadienal (**1b**) (□), 2*E*,4*E*-octadienal (**2a**) (◇), and 2*E*,4*Z*-octadienal (**2b**) (+), 2*E*,4*E*-heptadienal (**3a**) (△), 2*E*,4*Z*-heptadienal (**3b**) (▽).

Both isomers of 2,4-decadienal (**1ab**) were more active than their shorter-chain homologues, indicating the significance of chain length. The reduced activity of 2,4-octadienal (**2ab**) was also observed with purified material from *S. costatum*.[8] In all cases, the geometry at the C4-position of the double bond system of the α,β,γ,δ-unsaturated aldehydes had no influence on biological activity (Fig. 1) since the isomers were comparable in their threshold concentrations and IC_{50} for the inhibition of cell cleavage. To exclude the possible influence of isomerization or degradation during the assay period, we checked the stability of 2*E*,4*Z*-decadienal (**1b**) in seawater. If added as DMSO solution to filtered seawater in comparable concentrations to those used in the assay, 2*E*,4*Z*-decadienal (**1b**) (4*E*/*Z*>95/5) is stable over the 2–3 h assay period. Only slow isomerization to the thermodynamically more stable 2*E*,4*E*-decadienal (**1a**) is observed at 22°C with an isomeric composition of **1b** to **1a** (85/15) after 24 h. Thus the similar activity of the respective isomers in the bioassay is not due to their fast interconversion. In this context it is noteworthy, that *T. rotula* releases isomeric mixtures of 2*E*,4*E*/*Z*-decadienal **1ab**.[7] This seems to be the result of the biosynthesis and not of an abiotic isomerization, since both isomers are stable during the short time required for extraction and analysis.[22]

To evaluate if the observed biological activity is a general phenomenon with α,β,γ,δ-unsaturated dienals, we synthesized and tested both the 9-oxo-nona-5*E*/*Z*,7*E*-dienoic acid (**7a**,**b**) and the 12-oxo-dodeca-5*Z*,8*Z*,10*E*-trienoic acid (**6b**) previously identified from diatoms.[2,3] The trienoic acid **6b** reached an intermediate level of activity compared to 2,4-decadienal (**1ab**) and the unsaturated short-chain aldehydes (Fig. 2).

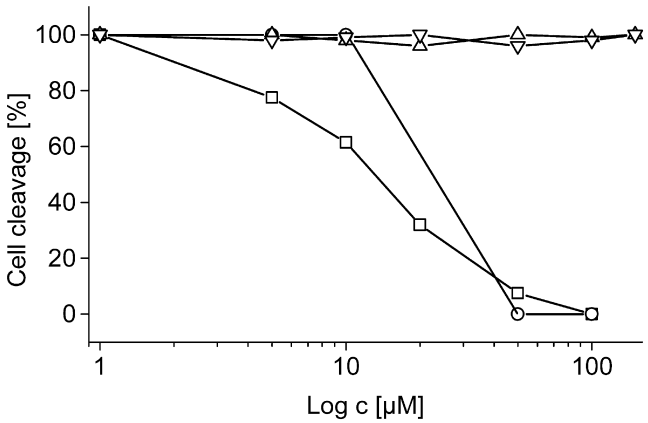


Figure 2. Inhibition of the first cell cleavage in sea urchin eggs by 13-oxo-trideca-9*Z*,11*E*-dienoic acid (**8b**) (□), 12-oxo-dodeca-5*Z*,8*Z*,10*E*-trienoic acid (**6b**) (○),[5] 9-oxo-nona-5*E*,7*E*-dienoic acid (**7a**) (▽), and 9-oxo-nona-5*Z*,7*E*-dienoic acid (**7b**) (△).

Surprisingly, both isomers of the shorter-chain homologue 9-oxo-nona-5*E*/*Z*,7*E*-dienoic acid (**7ab**) were not active, even at elevated concentrations. To verify if this lack of activity is a general feature of dienoic acids, we synthesized and tested the higher homologue 13-oxo-trideca-9*Z*,11*E*-dienoic acid (**8b**), not found in diatoms. The activity of this acid resembled that of the 12-oxo-dodeca-5*Z*,8*Z*,10*E*-trienoic acid (**6b**). The lack of activity of the 9-oxo-acid **7ab** is thus not a general feature of ω-oxo-dienoic acids but most likely attributable to an intramolecular interaction of the acidic group with the dienal terminus via a cyclic ring transition state, as suggested previously.[3] An interaction of the acidic group with the double bond system is also supported by the observation that 9-oxo-nona-5*Z*,7*E*-dienoic acid (**7b**) isomerised rapidly in seawater into the more stable **7a**. The half life of 2 h at 22°C is significantly shorter than that of 2*E*,4*Z*-decadienal (**1b**), a molecule which does not permit such an intramolecular interaction.

In diatoms aldehydes lacking the α,β,γ,δ-unsaturation are also found. Among those are mono-unsaturated aldehydes[7] and high abundances of saturated aldehydes.[5] The influence of the Michael-acceptor of the α,β,γ,δ-unsaturated aldehydes for the inhibitory activity was evaluated using different C10-derivatives (Fig. 3).

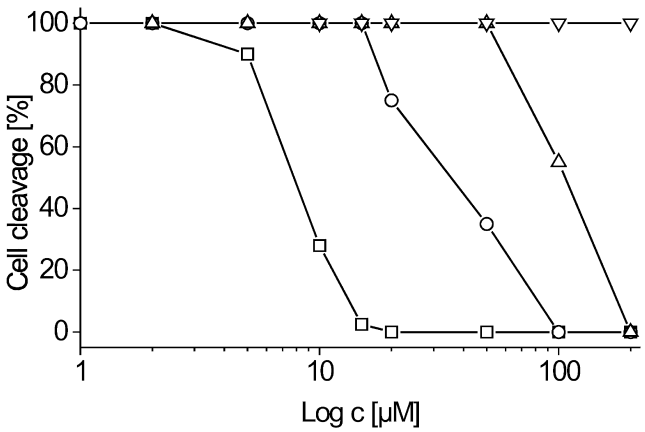


Figure 3. Inhibition of the first cell cleavage in sea urchin eggs by 2*E*-decenal (□), 4*Z*-decenal (○), decanal (△), and 2-decanone (▽).

Decanal, which lacks this Michael-acceptor structural element was active only at elevated concentrations. The same is true for 4*Z*-decenal, although the introduction of the additional double bond increases activity. In contrast, the Michael-acceptor 2*E*-decenal was among the most active molecules tested.

The overall importance of an aldehyde for biological activity is supported by the finding that 2-decanone is not active even at elevated concentrations. This was also the case for decanoic acid and 1-decanol. Other saturated aldehydes (C8 and C13[5]) exhibited lower activity compared to decanal.

3. Conclusion

The new synthesis of α,β,γ,δ-unsaturated aldehydes allowed to perform a detailed study of the structural elements contributing to their biological activity to inhibit sea urchin egg cleavage. Screening a series of diatom-derived oxylipins showed that the activity is related to the presence of a Michael-acceptor and not a specific feature of 2*E*,4*E*/*Z*-decadienal (**1ab**). Whether this activity is due to a covalent addition of nucleophiles, as suggested after model studies with **1a** and a deoxyadenosine derivative[23] has yet to be established. The minimum structural element required for activity is one double bond conjugated to the aldehyde functionality as in 2*E*-decenal. The geometry or even absence of the γ,δ-double bond is not determining for such activity. In contrast, the shorter chain length 2,4-dienals **2ab** and **3ab** had reduced activity as it was also the case for the acidic **7ab** and **8ab**. Polarity of the aldehydes thus seems to be an important feature influencing the biological activity.

4. Experimental

4.1. General remarks

Reactions were performed under Ar. Solvents and were dried according to standard methods. ^{1}H and ^{13}C NMR: Bruker Avance DRX 500 or AV 400 spectrometer. Chemical shifts of ^{1}H and ^{13}C NMR are given in ppm (δ) downfield relative to TMS. GCMS: Finnigan Trace MS equipped with an Alltech EC5 column, Helium as carrier. HR-MS: Micromass MasSpec (Micromass, Manchester, UK). HPLC: HP1100, equipped with a ChromSil ODS3 column. Preparative column chromatography was performed on Florisil (Sigma), or SiO_2 (ICN) 32-63, 60 Å. Reagents and solvents were purchased from Aldrich, Merck and Fluka.

4.2. Preparation of alkylzincates

23.1 mmol of the respective alkyl Grignard-compound in 30 mL THF were treated with 25.4 mmol $ZnBr_2$ in 40 mL THF at room temperature. After stirring for 30 min, the formed precipitate was allowed to settle and 48 mL of the supernatant were used for the coupling-reaction.

4.3. Co(II)-mediated coupling

0.77 mmol cobalt-(II)-acetylacetonate and 4.6 mmol LiBr were suspended in 20 mL THF before addition of 11.2 mL 1-methyl-2-pyrrolidone and 3.85 mmol 5-iodo-penta-2,4-dienal (**9b** or **9ab**) at room temperature. The reaction mixture was cooled to −30°C and 15.9 mmol alkylzicate or 7.95 mmol di-alkanoic acid ester-zinc-compound[20] were added. After 30 min the reaction mixture was warmed to 0°C in an ice-bath and hydrolysed with 200 mL of a saturated $NaHCO_3$ solution. The aqueous layer was extracted three times with diethylether and the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the products were purified by column chromatography.

4.4. Pd^0-mediated coupling

4.4.1. 2*E*,4*E*-Decadienal (1a). 0.04 mmol tetrakis(triphenylphosphine)palladium(0) and 0.7 mmol 5-iodo-penta-2,4-dienal (**9a** or **9ab**) were dissolved in 20 mL THF at −78°C and 2.9 mmol pentyl-zinc-bromide, dissolved in 30 mL THF were added. After 20 min at −78°C the reaction mixture was hydrolysed with 200 mL of saturated $NaHCO_3$ solution and the aqueous layer was extracted three times with diethylether. The combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the product purified by column chromatography on SiO_2 (petrol ether/ether 95/5) to give 84 mg (0.55 mmol, 79%) of **1a**.

4.5. Enzymatic saponification

0.53 mmol of the ester **7a**,**b** or **8b** were suspended in 100 mL 0.02 mol L^{-1} phosphate buffer (pH 7.2) by vigorous stirring at room temperature. After addition of 164 units of porcine liver esterase (PLE, Sigma) the

suspension was stirred for 1 h, washed with 10 mL petrol ether and pH 3 was adjusted with 10% sulphuric acid. The reaction mixture was extracted three times with diethylether and the combined organic phases were dried with Na_2SO_4. The solvent was removed under reduced pressure to give the pure (NMR, RP-HPLC) product.

4.6. Kinetic investigations of the isomerization

10 μL of a solution of **1b** or **7b** in DMSO (10 mg/mL) were added to 1 mL of filtered seawater. Decadienal **1a**,**b** was extracted by solid phase microextraction (SPME) on polydimethylsiloxane and the rearrangement was monitored by GC-MS (40°C for 2 min, 3°C min^{-1} to 110°C, 15°C min^{-1} to 280°C, hold for 2 min). The rearrangement of 9-oxo-5*Z*,7*E*-nonadionic acid **7b** was examined using HPLC-DAD (RP18 25% CH_3CN, 75% H_2O, 0.5% HOAc, 20 min to 100% CH_3CN, 5 min CH_3CN, 280 nm).

4.7. Bioassays

All non-synthesized compounds used in the assays were purchased at Sigma, (Deisenhofen, Germany) and purified by SiO_2 chromatography prior to use. **6b** was synthesized as described elsewhere.[2] The bioassays were performed according to a previously described procedure using solutions of the test compounds in DMSO that were added to seawater, the co-solvent DMSO had no influence on the assay.[5]

4.8. Spectroscopic data

The spectroscopic data for the aliphatic aldehydes **1ab**, **2a**, **3ab**,[13,24] and the ester of **7b**[3] match those from the literature.

4.8.1. 9-Oxo-nona-5*E*,7*E*-dienoic acid ethyl ester. ^{1}H NMR (d_6-benzene, 400 MHz) δ (ppm): 1.09 (t, J=7.1 Hz, 3H, $-CH_3$), 1.62 (m, 2H, C3), 1.89 (dt, J=7.6, 7.4 Hz, 2H, C4), 2.12 (t, J=7.4 Hz, 2H, C2), 4.07 (q, J=7.1 Hz, 2H, $-O-CH_2-$), 5.66 (dt, J=14.9, 7.2 Hz, 1H, C5), 5.86 (ddd, J=15.3, 11.0, 0.6 Hz, 1H, C6), 5.99 (dd, J=15.4, 7.7 Hz, 1H, C8), 6.53 (dd, J=15.4, 10.6 Hz, 1H, C7), 9.53 (d, J=7.8 Hz, 1H, C9). ^{13}C NMR (d_6-Benzene, 100 MHz) δ: 14.2 ($-CH_3$), 24.0 (C3), 32.3 (C4), 33.4 (C2), 60.1 ($-O-CH_2-$), 129.5 (C6), 130.9 (C8), 144.2 (C5), 150.8 (C7), 172.4 (C1), 192.3 (C9). EI-MS (70 eV) *m*/*z*: 66 (18), 67 (22), 77 (21), 79 (61), 81 (100), 104 (31), 107 (29), 108 (23), 122 (29), 150 (18), 196 (2). HR-MS: *m*/*z* calcd for $C_{11}H_{16}O_3$: 196.10995, found: 196.11062.

4.8.2. 9-Oxo-nona-5*E*,7*E*-dienoic acid (7a). ^{1}H NMR (CD_3OD, 400 MHz) δ: 1.79 (m, 2H, C3), 2.34 (t, J=7.3 Hz, 2H, C2), 2.40 (m, 2H, C4), 6.10 (dd, J=15.3, 8.0 Hz, 1H, C8), 6.30 (m, 2H, C5,6), 7.28 (dd, J=15.2, 9.7 Hz, 1H, C7), 9.50 (d, J=7.9 Hz, 1H, C9). ^{13}C NMR (CD_3OD, 100 MHz) δ: 25.2 (C3), 33.7 (C4), 34.4 (C2), 130.9 (C6), 131.6 (C8), 147.8 (C5), 155.2 (C7), 177.3 (C1), 196.4 (C9). EI-MS (70 eV) *m*/*z*: 53 (13), 67 (15), 77 (14), 81 (100), 91 (14), 95 (15), 104 (11), 108 (16), 122 (15), 150 (12), 168 (11). HR-MS: *m*/*z* calcd for $C_9H_{12}O_3$: 168.078644, found: 168.078590.

4.8.3. 13-Oxo-trideca-9*Z*,11*E*-dienoic acid methyl ester. ^{1}H NMR (d_8-THF, 400 MHz) δ: 1.24 (m, 6H, C4, C5, C6), 1.36 (m, 2H, C3), 1.48 (m, 2H, C7), 2.15 (t, J=7.4 Hz, 2H, C2), 2.26 (m, 2H, C8), 3.47 (s, 3H, $O-CH_3$), 5.86 (dt, J=10.7, 7.9 Hz, 1H, C9), 5.97 (dd, J=15.2, 7.9 Hz, 1H, C12), 6.17 (m, 1H, C10), 7.45 (ddd, J=15.2, 11.5, 0.9 Hz, 1H, C11), 9.53 (d, J=7.8 Hz, 1H, C13). ^{13}C NMR (d_8-THF, 100 MHz) δ: 29.3 (C3), 30.3–30.4 (C4–C8), 34.6 (C2), 51.5 ($O-CH_3$), 128.2 (C10), 133.5 (C12), 143.7 (C9), 146.7 (C11), 174.0 (C1), 193.4 (C13). EI-MS (70 eV) *m*/*z*: 55 (30), 67 (31), 79 (18), 81 (100), 95 (31), 109 (17), 121 (9), 149 (14), 178 (6), 238 (3). HR-MS: *m*/*z* calcd for $C_{14}H_{22}O_3$: 238.15747, found: 238.15690.

4.8.4. 13-Oxo-trideca-9*Z*,11*E*-dienoic acid (8a). ^{1}H NMR (d_8-THF, 400 MHz) δ: 1.24 (m, 6H, C4, C5, C6), 1.36 (m, 2H, C3), 1.47 (m, 2H, C7), 2.10 (t, J=7.4 Hz, 2H, C2), 2.26 (m, 2H, C8), 5.86 (dt, J=10.6, 7.9 Hz, 1H, C9), 5.96 (dd, J=15.2, 7.8 Hz, 1H, C12), 6.17 (m, 1H, C10), 7.41 (ddd, J=15.2, 11.5, 0.9 Hz, 1H, C11), 9.48 (d, J=7.8 Hz, 1H, C13). ^{13}C NMR (d_8-THF, 100 MHz) δ: 29.3 (C3), 30.3 (C4-C7), 30.5 (C8), 34.5 (C2), 128.1 (C10), 133.5 (C12), 143.7 (C9), 146.7 (C11), 174.7 (C1), 193.5 (C13). EI-MS (70 eV) *m*/*z*: 55 (29), 67 (30), 79 (17), 81 (100), 83 (40), 95 (33), 109 (17), 149 (29), 167 (14), 178 (13), 196 (8), 206 (12), 224 (17). HR-MS: *m*/*z* calcd for $C_{14}H_{22}O_3$: 224.141245, found: 224.141438.

4.8.5. 2*E*,4*Z*-Octadienal (2b). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.96 (t, J=7.4 Hz, 3H, C8), 1.50 (m, 2H, C7), 2.33 (ddt, J=8.8, 7.6, 1.4 Hz, 2H, C6), 6.01 (dt, J=11.8, 7.9 Hz, 1H, C5), 6.15 (dd, J=15.2, 7.9 Hz, 1H, C2), 6.29 (m, 1H, C4), 7.45 (ddd, J=15.3, 11.5, 1.0 Hz, 1H, C3), 9.61 (d, J=8.1 Hz, 1H, C1). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.4 (C8), 22.2 (C7), 30.1 (C6), 126.6 (C4), 131.4 (C2), 143.5 (C5), 146.5 (C3), 193.7 (C1). EI-MS (70 eV) *m*/*z*: 53 (13), 67 (16), 81 (100), 95 (10), 124 (17). HR-MS: *m*/*z* calcd for $C_8H_{12}O$: 124.088815, found: 124.088796.

Acknowledgements

We thank Professor W. Boland for the helpful discussion during the preparation of this work. We are grateful to the divers at the Roscoff Marine Station for providing the sea urchin samples. This work was supported by the Max-Planck Gesellschaft, CNRS and the PROCOPE-EGIDE program.

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