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COMMUNICATION

Stereoselective synthesis and hormonal activity of novel dafachronic acids and naturally occurring steroids isolated from corals†

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A stereoselective synthesis of (25*S*)- Δ^1 -, (25*S*)- $\Delta^{1,4}$ -, (25*S*)- $\Delta^{1,7}$ -, (25*S*)- $\Delta^{8(14)}$ -, (25*S*)- $\Delta^{4,6,8(14)}$ -dafachronic acid, methyl (25*S*)- $\Delta^{1,4}$ -dafachronate and (25*S*)-5 α -hydroxy-3,6-dioxocholest-7-en-26-oic acid is described. (25*S*)- $\Delta^{1,4}$ -Dafachronic acid and its methyl ester are natural products isolated from corals and have been obtained by synthesis for the first time. (25*S*)-5 α -Hydroxy-3,6-dioxocholest-7-en-26-oic acid represents a promising synthetic precursor for cytotoxic marine steroids.

The genes *daf-9* and *daf-12* play a key role in controlling the life cycle and longevity of the nematode *Caenorhabditis elegans*.^{1,2} It was found that *daf-9* encodes a cytochrome P450 oxidase which completes the synthesis of dafachronic acids **1** and **2** (Fig. 1). These steroidal acids are ligands for the hormone receptor DAF-12.³ By binding of dafachronic acids, DAF-12 is inactivated and the nematodes undergo normal reproductive development. In the absence of these ligands, DAF-12 is activated and dauer larvae are generated.²

Due to their hormonal activity and the importance for investigations in developmental biology, several synthetic routes have been reported for the dafachronic acids.^{4–10} We have developed a highly efficient synthetic route to (25*S*)- Δ^4 -dafachronic acid (**1**) and (25*S*)- Δ^7 -dafachronic acid (**2**).^{6,10} A crucial intermediate for our approach is the orthogonally diprotected diol **4** which has

Fig. 1 Steroidal ligands for the hormonal DAF-12 receptor of *C. elegans*.

been prepared from 3 β -hydroxychole-5-en-24-oic acid (**3**) in 8 steps and 66% overall yield using an Evans aldol reaction as key step (Scheme 1).⁶ With **4** as relay compound both hormonally active dafachronic acids became readily accessible. Desilylation of **4**, Oppenauer oxidation with isomerization of the double

Scheme 1 Synthesis of (25*S*)- Δ^4 - and (25*S*)- Δ^7 -dafachronic acid (**1**) and (**2**) and (25*S*)-dafachronic acid (**5**) using the orthogonally diprotected diol **4** as relay compound. *Reagents and conditions*: (a) 1.5 equiv. TBAF, THF, reflux, 17 h, 92%; (b) 1.5 equiv. Al(OiPr)₃, acetone–toluene (1 : 9), 100 °C, 5 h, 86%; (c) 2.0 equiv. NaOMe, MeOH, rt, 5 d, 87%; (d) 5.0 equiv. Jones reagent, 0 °C, 2 h, 85%; (e) 1.5 equiv. TBAF, THF, reflux, 17 h; (f) 4.0 equiv. LiAlH₄, THF, rt, 16 h, 93% for two steps; (g) 10% Pd/C, H₂, MeOH–CH₂Cl₂ (1 : 1), rt, 24 h, 99%; (h) 5.0 equiv. Jones reagent, acetone, 0 °C, 60 min, 88%; (i) 4.0 equiv. PDC, 8.0 equiv. *t*BuOOH, Celite®, benzene, 0 °C to rt, 41 h, 75%; (j) 10% Pd/C, H₂, EtOAc, rt, 16 h, 95%; (k) 1.3 equiv. L-Selectride®, THF, –78 °C, 1.5 h, 90%; (l) 5.0 equiv. SOCl₂, pyridine, 0 °C, 40 min, 87%; (m) 1.5 equiv. TBAF, THF, reflux, 16 h; (n) 4.0 equiv. LiAlH₄, THF, 0 °C to rt, 17 h, 82% for two steps; (o) 5.0 equiv. Jones reagent, acetone, 0 °C, 90 min, 89%.

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†Electronic supplementary information (ESI) available: ¹H and ¹³C NMR spectra of compounds **9–11**, **13**, **16**, **20** and **23**. 2D NMR spectra (COSY, HSQC, HMBC and NOESY) of compound **20**. CCDC 867379 and 867380. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25394a

Scheme 2 Synthesis of (25S)-Δ¹-, (25S)-Δ¹,⁴- and (25S)-Δ¹,⁷-dafachronic acid (**9**), (**10**) and (**11**). *Reagents and conditions:* (a) 10 mol% Pd(OCOCF₃)₂, 10 mol% DMSO, O₂, HOAc, 80 °C, 24 h, 93% **9**, 75% **10**, 86% **11**.

bond, cleavage of the pivalate and Jones oxidation led to (25S)-Δ⁴-dafachronic acid (**1**) in an improved 39% overall yield (12 steps). Alternatively, sequential removal of both protecting groups of compound **4** by desilylation with TBAF and subsequent cleavage of the pivalate *via* reduction using lithium aluminium hydride, catalytic hydrogenation of the double bond and Jones oxidation provided the unnatural (25S)-dafachronic acid (**5**) (12 steps, 53% overall yield). For the synthesis of (25S)-Δ⁷-dafachronic acid (**2**), the double bond of the orthogonally diprotected diol **4** was moved from the 5,6- to the 7,8-position *via* the following four-step sequence. Allylic oxidation at C-7 to the enone **6**, hydrogenation of the 5,6-double bond, stereoselective reduction to the 7α-alcohol **7** and finally, elimination of water afforded compound **8**. Removal of both protecting groups of **8** (first of the silyl and then of the pivaloyl group) followed by Jones oxidation provided (25S)-Δ⁷-dafachronic acid (**2**) in 15 steps and 27% overall yield.

Herein, we describe an efficient synthesis of novel dafachronic acids and of naturally occurring steroidal acids which have been isolated from corals. A first investigation of their hormonal activity is also presented. Using the palladium(II)-catalyzed process reported by Stahl *et al.* 3-oxosteroids can be regioselectively dehydrogenated at the 1,2-position.¹¹ Thus, (25S)-dafachronic acid (**5**), (25S)-Δ⁴-dafachronic acid (**1**) and (25S)-Δ⁷-dafachronic acid (**2**) have been transformed directly into (25S)-Δ¹-dafachronic acid (**9**), (25S)-Δ¹,⁴-dafachronic acid (**10**) and (25S)-Δ¹,⁷-dafachronic acid (**11**) in yields ranging from 75 to 93% (Scheme 2).^{‡11} In this context, it is noteworthy that compound **10** was recently described as a natural product. Namikoshi *et al.* isolated (25S)-3-oxocholesta-1,4-dien-26-oic acid (**10**) from the Indonesian soft coral *Minabea* sp.¹² Thus, our present route also constitutes the first synthesis of this natural product.

In an alternative approach to (25S)-Δ¹,⁴-dafachronic acid (**10**), (25S)-Δ⁴-dafachronic acid (**1**) was initially converted to the corresponding methyl ester **12** (Scheme 3). Dehydrogenation with 1.3 equiv. 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of *tert*-butyldimethylsilyl chloride (TBSCl)

Scheme 3 Synthesis of **13** and (25S)-Δ¹,⁷-dafachronic acid (**10**). *Reagents and conditions:* (a) cat. H₂SO₄, MeOH, reflux, 7 h, 96%; (b) 1.3 equiv. DDQ, 5 mol% TBSCl, dioxane, rt, 24 h, 65% (20% **12**); (c) 3.0 equiv. LiOH, THF–MeOH–H₂O (1 : 1 : 1), rt, 24 h, 88%.

Scheme 4 Synthesis of (25S)-Δ⁸(14)-dafachronic acid (**16**). *Reagents and conditions:* (a) PtO₂, H₂, EtOAc–HOAc (10 : 1), rt, 2 d, 94%; (b) 1.5 equiv. TBAF, THF, rt, 24 h; (c) 2.0 equiv. LiAlH₄, THF, 0 °C to rt, 8 h, 93% for two steps; (d) 5.0 equiv. Jones reagent, acetone, 0 °C, 2 h, 78%.

afforded the cross-conjugated dienone **13** in 65% yield along with 20% of starting material.^{‡13} The course of this reaction is much more difficult to control as compared to the procedure described by Stahl *et al.* Use of larger amounts of DDQ by over-oxidation led to methyl (25S)-Δ¹,⁴,⁶-dafachronate. Interestingly, methyl (25S)-Δ¹,⁴-dafachronate (**13**) also represents a natural product. A few years ago, Zubía *et al.* isolated methyl 3-oxocholesta-1,4-dien-26-oate from the Antarctic octocoral *Anthomastus bathyproctus*.¹⁴ However, they left the configuration at C-25 of their natural product undetermined. A comparison of the value reported by Zubía *et al.* for the ¹³C NMR signal of C-27 (δ = 17.0 ppm)¹⁴ with the value we have observed for C-27 of compound **13** (δ = 17.23 ppm) led us to assign an *S* configuration for C-25 of natural methyl 3-oxocholesta-1,4-dien-26-oate. Our assignment is based on the distinct difference found between the ¹³C NMR signals for C-27 of the (25S) and the (25R) series: This difference is observed for the carboxylic acids (compare Table 2 in ref. 10) as well as for the esters.^{5b,6b}

Starting from **8**, we synthesised (25S)-Δ⁸(14)-dafachronic acid (**16**) (Scheme 4). Isomerisation of the double bond provided quantitatively the diprotected Δ⁸(14)-compound **14**.¹⁵ Cleavage of first the silyl and then the pivaloyl protecting group led to the Δ⁸(14)-steroiddiol **15**. The regio- and the stereochemistry of **15** has been confirmed by an X-ray crystal structure determination (Fig. 2).[§] Finally, Jones oxidation afforded (25S)-Δ⁸(14)-dafachronic acid (**16**) in 16 steps and 25% overall yield based on **3**.[‡]

In a further study, we investigated the chemistry of a corresponding B-ring diene 3β,26-steroid diol resembling vitamin D.¹⁶ Starting from enone **6**, an additional double bond at position 7,8 was introduced *via* the Shapiro reaction (Scheme 5).¹⁷ Conversion of **6** to the tosylhydrazone **17** followed by treatment with an excess of lithium hydride provided the 5,7-diene **18**.

Fig. 2 Molecular structure of (25*S*)-cholest-8(14)-en-3 β ,26-diol (**15**) in the crystal (ORTEP plot at the 50% probability level).

Fig. 3 Molecular structure of (25*S*)-cholesta-5,7-diene-3 β ,26-diol (**19**) in the crystal (ORTEF plot at the 50% probability level).

Scheme 5 Synthesis of (25*S*)- $\Delta^{4,6,8(14)}$ -dafachronic acid (**23**). *Reagents and conditions:* (a) 7.5 equiv. *p*-toluenesulfonyl hydrazide, THF, reflux, 24 h, 81%; (b) 100 equiv. LiH, toluene, 100 °C, 4 h, 66%; (c) 3.0 equiv. TBAF, THF, rt, 24 h, 90%; (d) 1.2 equiv. LiAlH₄, Et₂O–CH₂Cl₂ (1 : 1), 0 °C to rt, 4 h, 84%; (e) 5.0 equiv. Jones reagent, acetone, 0 °C, 30 min, 50%; (f) 1.5 equiv. LiAlH₄, CH₂Cl₂–Et₂O (1 : 1), 0 °C to rt, 3 h, 100%; (g) 1.3 equiv. 4-phenyl-1,2,4-triazoline-3,5-dione, CH₂Cl₂, rt, 30 min, 86%; (h) 5.0 equiv. Jones reagent, acetone, 0 °C, 30 min, 75%.

Removal of the silyl and then the pivaloyl protecting group afforded (25*S*)-cholesta-5,7-diene-3 β ,26-diol (**19**). At this stage, the structural assignment has been additionally confirmed by X-ray analysis of single crystals of **19** (Fig. 3).[¶] Jones oxidation of compound **19** generated as expected the ketone at C-3 and the carboxylic acid at C-26. However, an additional dioxygenation of the 5,6-double bond led to (25*S*)-5 α -hydroxy-3,6-dioxocholest-7-en-26-oic acid (**20**).[‡] This structural assignment has been confirmed by extensive 2D NMR experiments (Fig. 4 and ESI[†]). It is noteworthy that Shin *et al.* have isolated bioactive steroids from the gorgonian *Acalycigorgia inermis* with structural features very similar to compound **20**.¹⁸ The synthesis of these natural products is currently in progress in our laboratories. Cleavage of the pivalate of the 5,7-diene **18** led to compound **21** which on Diels–Alder cycloaddition with 4-phenyl-1,2,4-

Fig. 4 NOESY spectrum of compound **20** (600 MHz, CDCl₃).

triazoline-3,5-dione (PTAD) afforded the adduct **22**.¹⁹ Jones oxidation of **22** proceeded with concomitant elimination of the heterocycle and provided directly (25*S*)- $\Delta^{4,6,8(14)}$ -dafachronic acid (**23**).[‡]

Finally, we have tested the hormonal activity of the novel (25*S*)-dafachronic acids in rescuing worms from dauer arrest. The details of our bioassay protocol have been described previously.^{5b,6b} Mutant worms *daf-9(dh-6)* are lacking the DAF-9 activity. Therefore, they cannot produce the ligands for the DAF-12 receptor and arrest as dauer larvae. Feeding of *daf-9(dh-6)* mutant worms with the (25*S*)-dafachronic acids described above led to a rescue from dauer arrest and to the development of adults. The ability to rescue the *daf-9(dh-6)* mutant worms from dauer arrest and to induce normal development of adults varies significantly for the different (25*S*)-dafachronic acids (Fig. 5).

The activity of the (25*S*)-dafachronic acids is dependent on the location of the double bond(s). The most active compounds are (25*S*)- $\Delta^{1,7}$ -dafachronic acid (**11**) and (25*S*)- Δ^7 -dafachronic acid (**2**) with a double bond at the 7,8-position as a common structural feature. They induce normal development of the worms already at concentrations below 10 nM. (25*S*)- Δ^1 -Dafachronic acid (**9**), (25*S*)- Δ^4 -dafachronic acid (**1**) and (25*S*)- $\Delta^{1,4}$ -dafachronic acid (**10**) belong to the group of second most active

Fig. 5 Hormonal activity of the different daifachronic acids.

compounds which at concentrations of 50 nM effect a rescue from dauer arrest for about 60–80% of the worms. (25S)- $\Delta^{4,6,8(14)}$ -Dafachronic acid (**23**) and (25S)- $\Delta^{8(14)}$ -dafachronic acid (**16**) are the least active compounds in this series. Previously, we have shown that (25S)-dafachronic acid (**5**) has about the same activity as (25S)- Δ^4 -dafachronic acid (**1**).^{6b,10} The present results emphasise the importance of the double bond at position 7,8 for the hormonal activity of dafachronic acids.

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Notes and references

‡ Spectroscopic data for (25S)- Δ^1 -dafachronic acid (**9**): Colourless crystals, mp 112–115 °C; ^{13}C NMR and DEPT (125 MHz, CDCl_3): δ = 12.17 (CH_3), 12.95 (CH_3), 17.00 (CH_3), 18.56 (CH_3), 21.22 (CH_2), 23.70 (CH_2), 24.08 (CH_2), 27.63 (CH_2), 28.20 (CH_2), 31.28 (CH_2), 34.01 (CH_2), 35.62 (CH), 35.64 (CH), 35.69 (CH_2), 38.96 (C), 39.26 (CH), 39.76 (CH_2), 40.98 (CH_2), 42.70 (C), 44.28 (CH), 49.91 (CH), 56.10 (CH), 56.33 (CH), 127.32 (CH), 158.68 (CH), 181.95 (C=O), 200.39 (C=O); anal. calc. for $\text{C}_{27}\text{H}_{42}\text{O}_3$: C 78.21, H 10.21; found: C 77.61, H 10.35.

Spectroscopic data for (25S)- $\Delta^{1,4}$ -dafachronic acid (**10**): Light yellow crystals, mp 129–130 °C; ^{13}C NMR and DEPT (125 MHz, CDCl_3): δ = 12.03 (CH_3), 17.02 (CH_3), 18.49 (CH_3), 18.65 (CH_3), 22.84 (CH_2), 23.69 (CH_2), 24.35 (CH_2), 28.09 (CH_2), 32.92 (CH_2), 33.67 (CH_2), 33.99 (CH_2), 35.49 (CH), 35.56 (CH), 35.64 (CH_2), 39.28 (CH), 39.45 (CH_2), 42.64 (C), 43.66 (C), 52.34 (CH), 55.41 (CH), 55.94 (CH), 123.71 (CH), 127.37 (CH), 156.20 (CH), 169.69 (C), 181.97 (C=O), 186.56 (C=O); anal. calc. for $\text{C}_{27}\text{H}_{40}\text{O}_3$: C 78.60, H 9.77; found: C 78.70, H 9.85.

Spectroscopic data for (25S)- $\Delta^{1,7}$ -dafachronic acid (**11**): Colourless crystals, mp 100–102 °C; ^{13}C NMR and DEPT (125 MHz, CDCl_3): δ = 11.92 (CH_3), 12.60 (CH_3), 17.03 (CH_3), 18.74 (CH_3), 21.55 (CH_2), 22.86 (CH_2), 23.76 (CH_2), 27.87 (CH_2), 28.56 (CH_2), 34.01 (CH_2), 35.64 (CH_2), 36.03 (CH), 37.37 (C), 39.27 (CH_2 and CH), 39.64 (CH), 40.11 (CH_2), 43.54 (C), 45.24 (CH), 55.15 (CH), 55.97 (CH), 117.83 (CH), 127.13 (CH), 138.67 (C), 157.43 (CH), 181.71 (C=O), 199.90 (C=O).

Spectroscopic data for methyl (25S)- $\Delta^{1,4}$ -dafachronate (**13**): Light yellow crystals, mp 75–80 °C; ^{13}C NMR and DEPT (75 MHz, CDCl_3): δ = 12.03 (CH_3), 17.23 (CH_3), 18.48 (CH_3), 18.67 (CH_3), 22.84 (CH_2), 23.79 (CH_2), 24.35 (CH_2), 28.08 (CH_2), 32.91 (CH_2), 33.67 (CH_2), 34.27 (CH_2), 35.51 (CH), 35.55 (CH), 35.65 (CH_2), 39.47 (CH_2), 39.50 (CH), 42.65 (C), 43.62 (C), 51.43 (CH_3), 52.36 (CH), 55.43 (CH), 55.98 (CH), 123.75 (CH), 127.42 (CH), 156.00 (CH), 169.44 (C), 177.37 (C=O), 186.44 (C=O); anal. calc. for $\text{C}_{28}\text{H}_{42}\text{O}_3$: C 78.83, H 9.92; found: C 78.94, H 9.77.

Spectroscopic data for (25S)- $\Delta^{8(14)}$ -dafachronic acid (**16**): Colourless crystals, mp 138–140 °C; ^{13}C NMR and DEPT (125 MHz, CDCl_3): δ = 11.93 (CH_3), 16.99 (CH_3), 18.25 (CH_3), 18.97 (CH_3), 20.05 (CH_2), 23.59 (CH_2), 25.89 (CH_2), 27.01 (CH_2), 29.14 (CH_2), 29.29 (CH_2), 34.04 (CH_2), 34.27 (CH), 35.54 (CH_2), 36.94 (CH_2), 37.11 (C), 38.04 (CH_2), 38.24 (CH_2), 39.34 (CH), 42.74 (C), 44.66 (CH_2), 46.39 (CH), 48.74 (CH), 56.79 (CH), 125.41 (C), 143.45 (C), 182.50 (C=O), 212.35 (C=O); anal. calc. for $\text{C}_{27}\text{H}_{42}\text{O}_3$: C 78.21, H 10.21; found: C 78.30, H 10.28.

Spectroscopic data for (25S)-5 α -hydroxy-3,6-dioxocholest-7-en-26-oic acid (**20**): Light yellow crystals; ^{13}C NMR and DEPT (150 MHz, CDCl_3): δ = 12.48 (CH_3), 15.86 (CH_3), 17.04 (CH_3), 18.72 (CH_3), 22.06 (CH_2), 22.51 (CH_2), 23.69 (CH_2), 27.66 (CH_2), 31.97 (CH_2), 33.96 (CH_2), 35.52 (CH_2), 35.81 (CH), 37.35 (CH_2), 38.83 (CH_2), 39.18 (CH), 40.83 (C), 43.71 (CH), 44.63 (C), 44.83 (CH_2), 55.74 (CH), 56.11 (CH), 79.87 (C), 119.53 (CH), 165.89 (C), 181.43 (C=O), 197.03 (C=O), 210.18 (C=O).

Spectroscopic data for (25S)- $\Delta^{4,6,8(14)}$ -dafachronic acid (**23**): Yellow crystals, mp 147–150 °C; ^{13}C NMR and DEPT (125 MHz, CDCl_3): δ = 16.62 (CH_3), 17.03 (CH_3), 18.74 (CH_3), 18.80 (CH_3), 18.95 (CH_2), 23.58 (CH_2), 25.30 (CH_2), 27.16 (CH_2), 33.98 (CH_2), 34.03 (CH_2), 34.07 (CH_2), 34.40 (CH), 35.43 (CH_2), 35.63 (CH_2), 36.73 (C), 39.36 (CH), 44.12 (CH), 44.21 (C), 55.54 (CH), 122.90 (CH), 124.38 (CH), 124.45 (C), 134.09 (CH), 156.09 (C), 164.60 (C), 182.42 (C=O), 199.77 (C=O).

§ Crystal data for (25S)-cholest-8(14)-en-3 β ,26-diol (**15**): $\text{C}_{27}\text{H}_{46}\text{O}_2$, crystal size: $0.28 \times 0.25 \times 0.19 \text{ mm}^3$, $M = 402.64 \text{ g mol}^{-1}$, monoclinic, space group: $P2_1$, $\lambda = 0.71073 \text{ \AA}$, $a = 11.0257(6) \text{ \AA}$, $b = 7.5583(4) \text{ \AA}$, $c = 14.7907(9) \text{ \AA}$, $\beta = 95.487(4)^\circ$, $V = 1226.94(12) \text{ \AA}^3$, $Z = 2$, $\rho_c = 1.090 \text{ g cm}^{-3}$, $\mu = 0.066 \text{ mm}^{-1}$, $T = 198(2) \text{ K}$, θ range = $1.38\text{--}29.48^\circ$, reflections collected: 27556, independent: 6718 ($R_{\text{int}} = 0.0672$), 274 parameters. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 ; final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0442$, $wR^2 = 0.0837$; maximal residual electron density: $0.133 \text{ e \AA}^{-3}$. CCDC 867379.

¶ Crystal data for (25S)-cholesta-5,7-diene-3 β ,26-diol (**19**): $\text{C}_{27}\text{H}_{44}\text{O}_2$, crystal size: $0.63 \times 0.15 \times 0.04 \text{ mm}^3$, $M = 400.62 \text{ g mol}^{-1}$, monoclinic, space group: $P2_1$, $\lambda = 0.71073 \text{ \AA}$, $a = 11.658(3) \text{ \AA}$, $b = 6.105(2) \text{ \AA}$, $c = 17.568(5) \text{ \AA}$, $\beta = 106.10(2)^\circ$, $V = 1201.3(6) \text{ \AA}^3$, $Z = 2$, $\rho_c = 1.108 \text{ g cm}^{-3}$, $\mu = 0.067 \text{ mm}^{-1}$, $T = 150(2) \text{ K}$, θ range = $1.21\text{--}27.00^\circ$, reflections collected: 18278, independent: 5131 ($R_{\text{int}} = 0.1437$), 274 parameters. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 ; final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0534$, $wR^2 = 0.0850$; maximal residual electron density: $0.160 \text{ e \AA}^{-3}$. CCDC 867380.

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