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Total synthesis of paracentrone, C_{31}-allenic *apo*-carotenoid†

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The stereocontrolled total synthesis of a C_{31}-allenic *apo*-carotenoid, paracentrone, was achieved by the convergent $C_{20} + C_{11} = C_{31}$ strategy. The key elements of our synthesis were the Pd-catalyzed cross-coupling to stereoselectively construct the conjugated polyene backbone skeleton and the designed geometrical isomerization at the central double bond of the conjugated polyene chain. In addition, the terminal oxygenated cyclohexane ring having the allenic moiety was prepared by the highly diastereoselective Sharpless epoxidation under our own reaction conditions.

Paracentrone (**1**) has been isolated from the sea urchin *Paracentrous lividus*[1] and the structure of this unique molecule was determined by Weedon and co-workers in 1969. This molecule is a C_{31}-*apo*-carotenoid, displaying a dihydroxycyclohexylidene allenic moiety at one terminal and a methyl ketone group at the other (Fig. 1).[2] It has been postulated that the naturally occurring paracentrone (**1**) is produced by the degradation of C_{40}-carotenoids, fucoxanthin or amarouciaxanthin A, in animals.[3] The first synthesis of paracentrone (**1**) was achieved by Haugan in 1996 over 13 linear steps from the readily available (3*R*,5*R*)-actinol (**7**) with the $C_{15} + C_{10} + C_5 + C_1 = C_{31}$ strategy.[4]

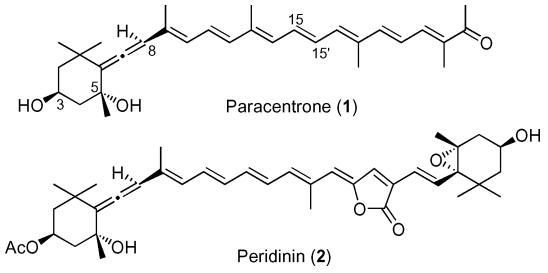


Fig. 1 Paracentrone (**1**) and peridinin (**2**).

Our longstanding interest in carotenoids and related natural products[5,6] led to the achievement of the stereocontrolled and convergent total synthesis of peridinin (**2**), a polyfunctional C_{37}-allenic *nor*-carotenoid.[7] Based on this synthesis, we have started to develop a new stereocontrolled synthetic strategy for naturally occurring allenic carotenoids.[8] In this communication, we disclose the stereocontrolled total synthesis of the C_{31}-allenic *apo*-carotenoid, paracentrone (**1**), using the convergent $C_{20} + C_{11} = C_{31}$ strategy.

The retrosynthetic disconnection at the C(15)–C(15′) position, which is the central part of the conjugated olefin, led to two fragments; the C_{20}-allenic triol **3** and the C_{11}-trienol **4** (Fig. 2). We envisioned that the former would be provided from acetylene **5** and trienyl vinyl iodide **6** by employing the Sonogashira cross-coupling[9] and S_N2' hydride reduction.[10] The acetylene **5** was easily available from **7** *via* the Sharpless asymmetric epoxidation under the precise conditions established in our laboratory.[5b,7]

† Electronic supplementary information (ESI) available: general experimental details. See http://www.rsc.org/suppdata/ob/b5/b500316d/

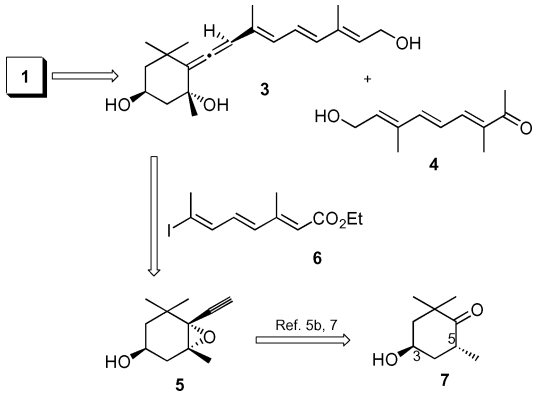
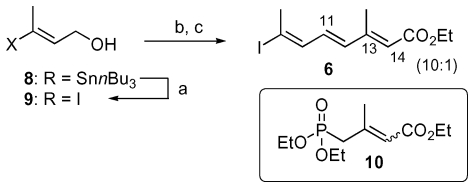


Fig. 2 Retrosynthetic analysis.

The preparation of trienyl iodide **6** was started from the known vinyl stannane **8**[11] using the modified de Lera's procedure (Scheme 1).[12] Vinyl stannane **8** was smoothly converted in high yield into the vinyl iodide **9** upon treatment with iodine in CH_2Cl_2. The addition of the carbanion derived from phosphonate **10**[13] to the corresponding aldehyde, prepared from **9**, in the presence of DMPU[14] gave the desired **6** in a highly stereoselective fashion (70% for two steps, 11*E* only, 13*E* : 13*Z* = 10 : 1 (carotenoid numbering)).



Scheme 1 Preparation of the trienyl iodide **6**. *Reagents and conditions*: (a) I_2, Na_2CO_3, CH_2Cl_2, 0 °C, 10 min, quant.; (b) MnO_2, Na_2CO_3, ether, rt, 2 h; (c) **10**, *n*BuLi, DMPU, THF, −20 °C, 5 min, 70% for two steps.

The Pd- and Cu-catalyzed Sonogashira reaction[9] between acetylene **5**[5b,7] and trienyl iodide **6** proceeded smoothly to furnish the desired coupling product **11**, with the complete retention of the stereochemistry, in 81% yield (Scheme 2). The reduction of **11** with DIBAL for the construction of the allenic moiety[10] afforded the C_{20}-allenic triol **3**,[15] which was oxidized into the corresponding aldehyde **12** (13*E* : 13*Z* = 10 : 1 (carotenoid numbering)) with Dess–Martin periodinane.[16] These C_{20}-allenic compounds **3** and **12** are not only the key intermediates for our paracentrone synthesis, but also the valuable half-fragments for the naturally occurring C_{40}-allenic carotenoids, for example fucoxanthin and neoxanthin (*vide infra*).

Meanwhile, the stereoselective preparation of the conjugated trienol **4** was also achieved by the consecutive Pd-catalyzed cross-coupling reactions. Carbon chain extension of the vinyl iodide **9** with (trimethylsilyl)acetylene under the Sonogashira conditions,[9] followed by the sequential desilylation and stannylcupration of the resulting terminal acetylene moiety[17] produced

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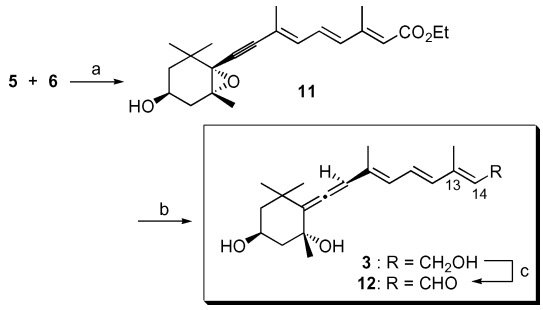
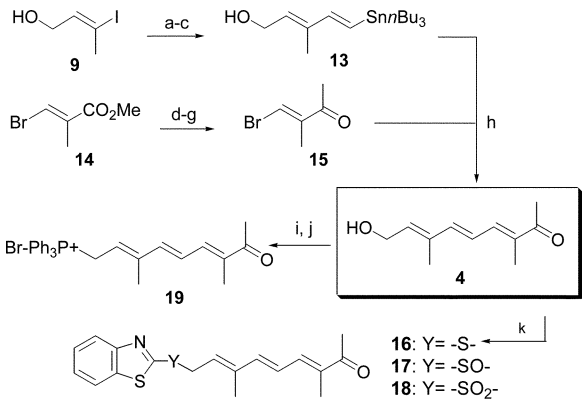


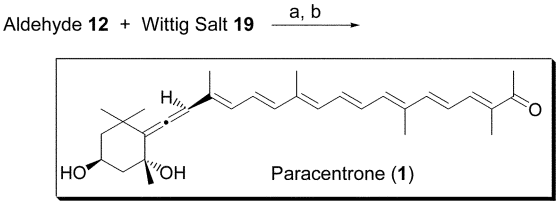
Scheme 2 Synthesis of the C_{20}-allenic triol **3** and aldehyde **12**. *Reagents and conditions*: (a) $Pd(PPh_3)_4$, CuI, iPr_2NH, rt, 4 h, 81%; (b) DIBAL, CH_2Cl_2, 0 °C, 30 min, 80%; (c) Dess–Martin periodinane, AcOEt, rt, 10 min.

the dienyl stannane **13** in 63% overall yield (Scheme 3). The vinyl bromide **15**, which is another component for **4**, was easily prepared from methyl bromomethacrylate **14**[18] by the simple functional group manipulation. The Stille coupling[19] between **13** and **15** in the presence of $Pd(PPh_3)_4$ and LiCl in DMF successfully afforded trienol **4**[20] bearing the desired all-*trans* stereochemistry in good yield.



Scheme 3 Synthesis of the trienol **4** and phosphonium salt **19**. *Reagents and conditions*: (a) (trimethylsilyl)acetylene, $Pd(PPh_3)_4$, CuI, Et_3N, THF, rt, 2 h; (b) K_2CO_3, MeOH, rt, 2 h, 78% for two steps; (c) $nBu_3Sn(nBu)CuCNLi_2$, THF, −30 °C, 1.5 h, 80%; (d) $LiAlH_4$, ether, rt, 1 h, quant.; (e) MnO_2, acetone, rt, 12 h; (f) MeMgBr, ether, rt, 30 min, 84% for two steps; (g) MnO_2, ether, rt, 12 h, 83%; (h) $Pd(PPh_3)_4$, LiCl, DMF, 75 °C, 1 h, 84%; (i) PBr_3, CH_2Cl_2, 0 °C, 10 min; (j) PPh_3, AcOEt, rt, 15 h, 74% for two steps; (k) 2-mercaptobenzothiazol, PPh_3, DEAD, THF, rt, 30 min, 77%.

With the C_{20}-allenic aldehyde **12** and the C_{11}-trienol **4** in hand, our attention turned to the fragment union by the olefination reaction. First, the conversion of trienol **4** into the corresponding benzothiazoyl sulfone **18** for the modified Julia–Kocienski reaction[21] was attempted, which was effectively utilized in our previous peridinin synthesis.[7] The trienol **4** was transformed into the corresponding benzothiazolyl sulfide **16** by the Mitsunobu reaction with 2-mercaptobenzothiazole and the oxidation of **16** into the corresponding sulfone **18** was tried by keeping the geometry of all the *E*-olefins. However, this transformation unfortunately failed and caused a significant *E*–*Z* isomerization of the double bond under sulfur-atom oxidation conditions. After numerous attempts, we knew that the isomerization occurred from the corresponding sulfoxide **17** resulting from the [2,3]-sigmatropic rearrangement.[22] On the other hand, the connection of the fragments was successfully achieved by the Wittig reaction, which is traditionally used in carotenoid synthesis. In this event, the trienol **4** was transformed into phosphonium salt **19** *via* the corresponding allylic bromide by the standard method. The Wittig condensation between **12** and **19** using NaH as a base proceeded at rt in the dark for three hours to afford a mixture of more than four isomers, including the major component in HPLC in 61% yield (Scheme 4). This was probably caused by the *E*/*Z* mixtures at the C(13) and C(15) positions. Fortunately, we found that the mixture gradually converged to the major isomer at rt in $CDCl_3$.[23] After one hour, the major isomer comprised nearly 70% of the products and was isolated by HPLC purification.[24] The spectral data of this isolated major isomer were in good agreement with those of the reported natural product.[4,25] Thus, we achieved the stereocontrolled total synthesis of the C_{31}-allenic *apo*-carotenoid, paracentrone (**1**), by the convergent $C_{20} + C_{11} = C_{31}$ strategy.



Scheme 4 Total synthesis of paracentrone. *Reagents and conditions*: (a) NaH, DME, CH_2Cl_2, rt, 3 h, 61%; (b) HPLC purification.[24]

In our achievement of the total synthesis of the allenic carotenoids, peridinin (**2**)[7] and paracentrone (**1**), we actually found that the central disubstituted double bond in the carotenoid molecules is easily isomerized from *cis* to *trans* in an acceptable ratio. These phenomena were also studied in detail in the field of spectroscopy, including the calculation of the electron distribution of the conjugated polyene systems.[26] Accordingly, the main subject for the stereocontrolled synthesis of the allenic carotenoids can be simplified based on how we synthesize the two fragments bisected at the central double bond in the polyene chain in a stereocontrolled manner. Based on these observations, we propose an effective $C_{20} + C_{20} = C_{40}$ strategy for the stereocontrolled synthesis of allenic carotenoids. This strategy would be generally applicable to the synthesis of widely occurring C_{40}-allenic carotenoids and is distinguishable from the previously employed $C_{15} + C_{10} + C_{15} = C_{40}$ one.[27]

Acknowledgements

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15 Data for **3**: $[\alpha]_D^{21}$ −23.47 (*c* 0.58, $CHCl_3$); IR (KBr, cm^{-1}) 3356, 2961, 2928, 2860, 1930, 1724, 1641, 1454, 1373, 1253, 1157, 1070; ^1H NMR (400 MHz, CD_3OD) δ 6.54 (dd, 1H, J = 15.1, 11.2 Hz), 6.27 (d, 1H, J = 15.1 Hz), 6.07 (d, 1H, J = 10.5 Hz), 6.02 (s, 1H), 5.64 (t, 1H, J = 6.8 Hz), 4.22 (d, 2H, J = 6.8 Hz), 4.20 (m, 1H), 2.18 (ddd, 1H, J = 12.7, 3.9, 2.0 Hz), 1.89 (ddd, 1H, J = 14.9, 3.9, 2.0 Hz), 1.83 (s, 3H), 1.80 (s, 3H), 1.50–1.20 (m, 2H), 1.33 (s, 3H), 1.33 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 203.4, 137.7, 137.2, 133.1, 131.8, 128.9, 125.8, 118.4, 103.6, 73.1, 64.7, 59.5, 50.6, 50.1, 36.6, 32.9, 31.4, 29.6, 14.2, 12.6; EI^+ HRMS found m/z 318.2193, calcd for $C_{20}H_{30}O_3$ M^+ 318.2194.

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20 Data for **4**: IR (KBr, cm^{-1}) 3430, 3054, 3000, 2922, 1647, 1607, 1435, 1395, 1366, 1319, 1290, 1233, 1171, 1096, 1073, 1030; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, 1H, J = 9.5 Hz), 6.62 (d, 1H, J = 15.1 Hz), 6.55 (dd, 1H, J = 15.1, 9.5 Hz), 5.87 (t, 1H, J = 6.6 Hz), 4.36 (d, 2H, J = 6.6 Hz), 2.36 (s, 3H), 1.92 (d, 3H, J = 1.2 Hz), 1.88 (d, 3H, J = 0.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 143.9, 139.6, 136.1, 135.6, 134.9, 123.8, 59.4, 25.5, 12.5, 11.6.

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22 The main pathway in the side-reactions would involve the [2,3]-sigmatropic rearrangement of the intermediate sulfoxide to the sulfenate ester, the details of which will be reported in a full account of this work. See:D. A. Evans and G. C. Andrew, *Acc. Chem. Res.*, 1974, **7**, 147.

23 The thermal isomerization from *cis* to *trans* at the central C(15)–C(15′) disubstituted double bond was also observed in our peridinin synthesis.[7] This feature was followed and detected by HPLC analysis, the details of which will be reported in a full account of this work.

24 Conditions: column: Develosil 60-5 (4.6 × 250 mm); mobile phase: THF–hexane–*i*PrOH = 15 : 67 : 3; flow rate: 1.0 ml min^{-1}; UV-detection: 450 nm; retention time: 22 min (all-*E*-isomer).

25 Data for paracentrone (**1**): IR (KBr, cm^{-1}) 3407, 2961, 2924, 2855, 1929, 1721, 1649, 1607, 1530, 1453, 1368, 1321, 1279, 1229, 1157, 1071, 1040, 992, 963; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (dq, 1H, J = 10.5, 1.0 Hz), 6.73 (dd, 1H, J = 14.2, 11.5 Hz), 6.66 (d, 1H, J = 14.9 Hz), 6.63 (dd, 1H, J = 14.1, 11.5 Hz), 6.60 (dd, 1H, J = 14.6, 11.5 Hz), 6.59 (dd, 1H, J = 15.4, 10.7 Hz), 6.39 (d, 1H, J = 11.5 Hz), 6.34 (d, 1H, J = 15.1 Hz), 6.26 (d, 1H, J = 11.0 Hz), 6.12 (d, 1H, J = 11.3 Hz), 6.03 (s, 1H), 4.32 (m, 1H), 2.36 (s, 3H), 2.27 (ddd, 1H, J = 13.3, 4.2, 1.9 Hz), 1.991 (s, 3H), 1.985 (s, 3H), 1.96 (m, 1H), 1.94 (d, 3H, J = 1.0 Hz), 1.81 (s, 3H), 1.41 (m, 1H), 1.35 (s, 3H), 1.33 (s, 3H), 1.35 (m, 1H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 199.4, 144.5, 139.9, 137.9, 137.0, 136.2, 135.5, 132.6, 132.3, 132.1, 129.4, 128.4, 125.6, 123.8, 117.7, 103.2, 73.0, 64.3, 49.5, 48.9, 35.8, 32.2, 31.4, 29.4, 25.6, 14.0, 12.9, 12.8, 11.7; ESI HRMS found m/z 461.3065, calcd for $C_{31}H_{42}O_3$ $[M - H]^-$ 461.3056.

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