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Synthesis of the C1–C12 Fragment of Calyculin C

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Dedicated to the memory of Professor István E. Markó.

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Abstract Calyculins are a class of highly cytotoxic metabolites originally isolated from the marine sponge Discodermia calyx. To date, a total of twelve different calyculins (A–J) and calyculinamides (A, B and F) have been described, the most abundant (in D. calyx) being calyculins A and C. Herein, we demonstrate a concise route to access the C1–C12 tetraene fragment of calyculin C using transition-metal-catalyzed coupling reactions (Suzuki–Miyaura, Stille, Negishi and Heck) for the key connections. The synthesis starts from propionaldehyde and proceeds in 10 steps with 7.5% overall yield. We also describe an efficient route for the preparation of (Z)-3-iodobut-2-enenitrile in four steps and 68% yield.

Key words calyculins, natural products, transition-metal-catalyzed cross-coupling, Suzuki–Miyaura, Stille, Negishi and Heck coupling, syntheses of di- and polyenes

Calyculins are a class of highly cytotoxic metabolites originally isolated from the marine sponge Discodermia calyx by Fusetani et al. Later, other marine sponges containing calyculins and calyculinamides were found. To date, a total of twelve different calyculins (A–J) and calyculinamides (A, B and F) have been described, the most abundant (in D. calyx) being calyculins A and C (Scheme 1), which differ from each other only by methyl substitution at C32. The remaining calyculins are either geometric isomers of the calyculins A or C, or close derivatives of calyculin A: calyculinamides, dephosphonocalyculin A, geometricin and swinhoeiamide, and clavosines A–C. Structure–activity relationships and biosyntheses of these sponge-derived cytotoxins have been reviewed.

These intriguing structures have inspired several research groups to devote significant synthetic efforts toward the calyculins, and these are summarized in Table 1.

We have been involved in the development of a synthetic access to calyculins and their analogues, and our chosen retrosynthesis is shown in Scheme 1. We have so far completed the syntheses of fragments A–C,15 and have reported a synthesis of the tetraene fragment D,16 but which unfortunately is not attractive for large-scale efforts. Previous syntheses of the tetraene fragment D have been reported by Barrett,17 Shioiri18 and Armstrong.19

Transition-metal-catalyzed alkenyl–alkenyl cross-coupling reactions have proven to be effective in stereoselective syntheses of di- and polyenes and have been successfully applied to the total syntheses of a wide variety of natural products.

Herein, we describe our recent results on the application of Pd-catalyzed cross-coupling reactions to the synthesis of the C1–C12 tetraene fragment D of calyculin C. We tested the effectiveness of Stille, Negishi, and Heck coupling reactions.

Table 1 Overview of the Reported Total Syntheses of Calyculins

<table>
<thead>
<tr>
<th>Group</th>
<th>Target</th>
<th>No. of steps</th>
<th>Overall yield</th>
<th>Remarks</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evans</td>
<td>ent-calyculin A</td>
<td>33</td>
<td>0.54%</td>
<td>total synthesis</td>
<td>9</td>
</tr>
<tr>
<td>Masamune</td>
<td>calyculin A</td>
<td>43</td>
<td>0.31%</td>
<td>total synthesis</td>
<td>10</td>
</tr>
<tr>
<td>Shioiri</td>
<td>calyculin A</td>
<td>32</td>
<td>0.092%</td>
<td>formal synthesis</td>
<td>11</td>
</tr>
<tr>
<td>Smith</td>
<td>ent-calyculin A</td>
<td>35</td>
<td>0.89%</td>
<td>formal synthesis</td>
<td>12</td>
</tr>
<tr>
<td>Armstrong</td>
<td>calyculin C</td>
<td>30</td>
<td>0.018%</td>
<td>total synthesis</td>
<td>13</td>
</tr>
<tr>
<td>Barrett</td>
<td>ent-calyculin A</td>
<td>34</td>
<td>0.9%</td>
<td>formal synthesis</td>
<td>14</td>
</tr>
</tbody>
</table>
Suzuki–Miyaura coupling strategies for the key connections of three precursors: iodonitrile 1, an appropriate component 2, 3 or 4 and alcohol 5 (Scheme 2).

The synthesis of iodonitrile 1 started with a one-pot Red-Al reduction of readily available 2-butyn-1-ol (6) followed by iodination to give alcohol 7.28 Oxidation of the primary alcohol 7 with MnO2 gave aldehyde 8, which was converted into oxime 9 (as a mixture of isomers) in 85% yield over the three steps. Initial attempts to convert 9 into iodonitrile 1 using (CF3CO)2O and imidazole or N-chlorosuccinimide and triphenylphosphine in CH2Cl2 proved unsuccessful. However, the desired conversion was achieved by treatment of 9 with thionyl chloride at 0 °C, providing (Z)-3-iodobut-2-enenitrile (1) as the only isomer in 68% overall yield in four steps (Scheme 3). The oximes 9 and iodonitrile 1 were found to be light- and temperature-sensitive but could be stored in a freezer in darkness for a long time (a year or more).

A Stille coupling was initially attempted in order to obtain adduct 11 (Scheme 4). Stannyl derivative 2 was prepared from propargylic alcohol (3) by several methods: a direct stannylcupration reaction with in situ generated Bu3Sn(Bu)CuCNLi2, a radical hydrostannylation reaction with Bu3SnH and AIBN at 80 °C, or a Pd(0)-catalyzed hydrostannylation reaction. Due to the formation of isomer mixtures, the yield of 2 obtained by these different methods varied from low to moderate, the best being obtained through direct stannylcupration. The large excess of toxic Bu3SnH required for full conversion of substrate 3, the low yield and the necessity to separate isomers made this approach unattractive. Therefore, the Stille coupling of iodonitrile 1 with 2, although giving 11 stereoselectively in 39% yield, was not optimized further.

The next attempt to prepare adduct 11 was through a Negishi coupling procedure. This alternative shorter route
included a one-pot Schwartz hydrozirconation of 3, transmetalation from Zr to Zn and a Pd-catalyzed cross-coupling of the vinylzinc intermediate 10 with iodonitrile 1 to provide 11 in 60% yield as a single isomer. Oxidation of 11 with MnO₂ afforded the conjugated aldehyde 12 in an excellent 90% yield (Scheme 4).

The Mizoroki–Heck cross-coupling reaction 33a,b is a much more attractive method providing conjugated aldehyde 12 directly from 1 in one step (Scheme 5). Unfortunately, initial experiments showed that the reaction of iodonitrile 1 with acrolein (4) at room temperature yielded an inseparable mixture of two isomeric compounds 12 and 13 (Table 2, entries 1–3). The isomeric compound was likely to be diene 13 because of the typical trans double bond coupling constant (J = 15.8 Hz) in the 1H NMR spectrum and the low possibility of the formation of branched Heck coupling products with olefins containing an electron-withdrawing carbonyl group, as found in acrolein. The only remaining possibility is the isomerization of the cyano group, which has been described previously.33c

Some reactions (Table 2, entries 1 and 5) gave high conversions (determined from the 1H NMR spectral data), but low isolated yields. A possible explanation is base-initiated iodine elimination in 1 and removal of volatile but-2-yne-nitrile from the reaction mixture. Reaction times that were too long led to contamination of the product with polymerization or Diels–Alder cyclization by-products. After screening different catalysts and bases, we were fortunate to find conditions delivering the desired isomer 12 with 95% isomeric purity and 85% yield (entry 9). The NMR data of this product were identical with those previously obtained for compound 12 prepared via different methods (Scheme 4).

Aldehyde 12 was next subjected to the Ramirez reaction 34 by treatment with the ylide formed in situ from triphenylphosphine and tetrabromomethane to give dibromide 14 (Scheme 6).

A Negishi-type reaction of dibromide 14 would require iodide 15, which was synthesized according to Scheme 7. Thus, alcohol 6 was reacted with Schwartz’s reagent and then iodinated leading to iodide 21. Silylation then gave the protected iodide 15. However, attempts to couple 14 with the Zn reagent derived from iodide 15 in the presence of Pd(PPh₃)₄ failed.

Alternatively, the Suzuki–Miyaura coupling of dibromide 14 and olefin 16 gave the corresponding tetraene 17 (Scheme 6). The synthesis of 16 is shown later in Scheme 11. Treatment of 17 with t-BuMe₂SiOTf and 2,6-lutidine in

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Table 2 Conditions Screened for the Mizoroki–Heck Cross-Coupling of Iodonitrile 1 with Acrolein (4) Affording Conjugated Aldehyde 12

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Base</th>
<th>12:13 Conversion (%)</th>
<th>Yield (%)</th>
<th>Time (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c</td>
<td>PdCl₂</td>
<td>K₂CO₃</td>
<td>53:47 full</td>
<td>36</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Ag₂CO₃</td>
<td>KOAc</td>
<td>73:27 15 NE</td>
<td>80</td>
<td>1</td>
</tr>
<tr>
<td>3d</td>
<td>AgOAc</td>
<td>KOAc</td>
<td>95:5 12 NE</td>
<td>80</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>AgOAc</td>
<td>KOAc</td>
<td>95:5 80 40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Pd(dba)₃</td>
<td>AgOAc</td>
<td>94:6 18 NE</td>
<td>99</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>Pd(acac)₂</td>
<td>–</td>
<td>95:5 95 65</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)₂</td>
<td>–</td>
<td>95:5 95 85</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>CsOAc</td>
<td>–</td>
<td>82:18 99</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*a* Conversions determined from the ¹H NMR spectra. NR = no reaction.

*b* Yield of isolated product. NE = not estimated.

*c* Bu₄NF (1 equiv) was added to the reaction mixture.

*d* Instead of acetonitrile the same amount of acrolein was added.

*e* 10 mol% Pd(OAc)₂ was used.
dichloromethane at –85 °C led to the protected compound 18 in 91% yield along with a small amount of cyclized compound 19. Unfortunately, compound 18 showed a tendency to undergo spontaneous cyclization to give compound 19 during column chromatography or on standing in solution at room temperature. This type of Pd-catalyzed cyclization of conjugated tetraenes has been reported by Parker,36 Trauner37 and Baldwin.38 Finally, the bromotetraene 18 was subjected to a Negishi cross-coupling using ZnMe₂ and [Pd(t-Bu3P)₂]39 to give tetraene 20.

As the approach to tetraene 20 was significantly complicated by the undesired formation of the cyclic compound 19, modifications according to Scheme 8 were undertaken to avoid the undesired cyclization.

The synthesis of the key compound 5 started with self-aldol condensation of propionaldehyde (23) catalyzed by 4-trans-hydroxy-L-proline in DMSO40 to give 24 as a 6:1 anti/syn diastereomeric mixture (determined by ¹H NMR) (Scheme 9). Unfortunately, the next step, silylation with tert-butyldimethylsilyl triflate and diisopropylethylamine in dichloromethane at 0 °C, was accompanied by partial racemization at the labile α-stereogenic center leading to compound 25 in 76% yield (2 steps from 23), but a diastereomeric ratio of 2:1 (anti/syn). The protected compound 25 was subjected to the Ramirez reaction and the dibromoolefins 26 and 27 were separated through column chromatography on silica gel to afford the desired diastereomer 26 as the major product. Dibromide 26 was then subjected to a Corey–Fuchs alkynylation step.41 Thus, elimination with n-butyllithium and methylation with iodomethane gave intermediate 28 in excellent yield. Sequential hydrozirconation of 28 with Schwartz’s reagent42 (obtained in situ from Cp₂ZrCl₂ and DIBAL-H) and iodination afforded iodide 29 in 65% yield.

The enantiomeric composition of the obtained chiral compounds was determined according to the Mosher method.43 Deprotection of 26 with n-Bu₄NF at 45–50 °C proceeded with dehydrobromination leading to monobromo-substituted 30. Improved results were obtained when 28 was deprotected under the same conditions to give the more stable compound 31 (Scheme 10), which was then subjected to derivatization with Mosher’s acid chlorides.44 NMR analysis established a 70% enantiomeric excess for alkyne 28 (see the Supporting Information).

Only a few approaches to the anti diastereomer of 24 or its precursors with high de and ee values, requiring multi-step syntheses, are described.45 When we first tested the key steps of the approach (see Scheme 8), we gave preference to the shorter synthetic route to compound 29 with lower ee over the longer synthetic route with higher ee.
In multistep syntheses a convergent strategy is much more advantageous over a linear one. We therefore prepared three compounds, 32, 16, and 21, and planned to modify them according to Scheme 11. A further intention was the Heck coupling of the obtained diene with 1 and final assembly of the resulting triene with key compound 5 (i.e., vinyl iodide 29) in the last step.

Only the tin derivative 34 was obtained with a satisfactory yield according to this scheme. All attempts to convert 34 into compound 37 by metathesis with 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane led to complex reaction mixtures with low yields of 37 (Scheme 12). The reaction of 34 with 1 resulted in formation of the Stille coupling product instead of the desired Heck coupling product.

The Pd(PPh3)4-catalyzed Suzuki–Miyaura coupling of vinylboronate 16 with iodide 29 proceeded stereoselectively with 95% yield to give the conjugated diene 38 with two trisubstituted double bonds (Scheme 13). Oxidation with MnO2 afforded aldehyde 39, which was subjected to Wittig olefination to yield the conjugated triene 40.

Inspired by the successful Mizoroki–Heck coupling of 1 with acrolein (4) (see Scheme 5), we first tried to apply the same conditions to couple triene 40 with iodonitrile 1 (Scheme 14). As AgOAc had demonstrated the best stereoselectivity in this reaction, we opted for AgOAc as the base again and no other bases were tested. However, the best conditions from Table 2 were not a guarantee of the desired result for the reaction of iodonitrile 1 with triene 40. All experiments yielded a mixture of isomers, which were not separated into individual components. One of the components was tetraene 41, the 1H NMR data of which were identical to those of the same compound obtained later through Suzuki–Miyaura coupling according to Scheme 15. Analysis of the spectral data of the second component most likely showed the formation of isomer 42 instead of 43.

Despite the lack of high stereoselectivity this reaction is interesting because, to the best of our knowledge, it is one of only a few examples of the Heck coupling of vinyl halides with nonaromatic trienes.47
nitrile 1 via a Suzuki–Miyaura coupling to afford the desired tetraene 41. The chemical shifts and coupling constants in the 1H NMR of the obtained tetraene 41 matched very well with the same parameters described previously for an analogous tetraene fragment.48

In summary, we have demonstrated a concise route to access the C1–C12 tetraene fragment 41 of calyculin C. The synthesis starts from propionaldehyde (23) and proceeds in 10 steps with 7.5% overall yield. We have also described an efficient route for the preparation of (Z)-3-iodobut-2-ene-nitrile (1) in four steps and 68% overall yield.

Moisture-sensitive reactions were carried out under an argon atmosphere, and glassware was flame-dried under high vacuum or in an oven. Dry solvents (THF, Et2O, toluene, MeCN, CH2Cl2) were obtained using an MBrue MB-SPS 800 solvent drying system. Commercial reagents were used without further purification. Ph3P was recrystallized from hot ethanol and was dried over P2O5, under vacuum. n-BuLi was titrated with N-benzylbenzamide. Other solvents and reagents were used as received. Analytical TLC was performed using Merck silica gel (60, F254 230–400 mesh) precoated aluminum plates and were used as received. Analytical TLC was performed using Merck silica gel (hexane/EtOAc, 5:1). The spectroscopic data are consistent with reported literature data.[49,50]

HRMS were obtained using a Waters Micromass LCT Premier (ESI) spectrometer.

Scheme 15 Final steps in the synthesis of tetraene 41 according to the second strategic plan

(Z)-3-Iodobut-2-en-1-ol (7)

A solution of Red-Al® (65% in toluene, 9 mL, = 3.5 M, 31.5 mmol) was added dropwise over 1 h to a solution of 2-butyn-1-ol (6) (1.59 g, 22.7 mmol) in dry Et2O (35 mL) at 0 °C under an inert atmosphere. The reaction mixture was allowed to warm slowly to r.t. and was stirred at ambient temperature overnight. After the starting material had been completely consumed (TLC monitoring), the mixture was cooled to 0 °C and EtOAc (1.8 mL) was added dropwise. The mixture was then cooled to –78 °C and a solution of I2 (8.65 g, 34.1 mmol) in THF (25 mL) was added dropwise over 1.5 h. After 30 min, the cooling bath was removed and stirring was continued at r.t. for 1 h. The mixture was then poured into an ice-cold saturated aqueous solution of Na2S2O3 and extracted with Et2O. The combined organic fractions were dried over Na2SO4, filtered and concentrated under reduced pressure (50 mbar) without heating. The residue was dissolved in CH2Cl2, r.t.

(Z)-3-Iodobut-2-enal Oxime (9)

To a solution of alcohol 7 (4.5 g) in CH2Cl2 (100 mL) was added MnO2 (22 g, 253 mmol) portionwise. When the reaction was complete, the MnO2 was removed by filtration through a pad of Celite® and the pad was rinsed with CH2Cl2. The filtrate was concentrated under reduced pressure (250 mbar) without heating. The residue was dissolved in THF (30 mL) and NH2OH.HCl (1.9 g, 27.3 mmol), H2O (7 mL) and NaHCO3 (1.9 g, 22.7 mmol) were added portionwise. The reaction mixture was stirred at r.t. for 20 min and then poured into a saturated aqueous solution of NaHCO3 and extracted with CH2Cl2. The combined organic fractions were dried over Na2SO4, filtered and concentrated under vacuum without heating. The residue was purified by column chromatography on silica gel (hexane/Et2O, 40:1 to 20:1) to
give 9 as a slightly yellow solid [4.0 g, 84% from 2-butyn-1-ol (6)]. This compound was very light-sensitive and should be stored in a freezer at −18 °C in the dark.

IR (thin film): 3160, 3042, 2865, 2772, 1633, 1478, 1423, 1309, 1261, 1080, 1015, 974, 839, 726 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 9.92 (br s, 1 H), 7.87 (d, J = 9.1 Hz, 0.62 H), 7.20 (d, J = 8.5 Hz, 0.34 H), 6.87 (d, J = 8.5 Hz, 0.34 H), 6.28 (ddd, J = 9.1, 1.4 Hz, 0.64 Hz), 2.71 (d, J = 1.5 Hz, 1.05 H), 2.66 (s, 1.93 H).

13C NMR (101 MHz, CDCl₃): δ = 154.96, 150.91, 127.86, 122.84, 113.02, 109.22, 35.33, 34.95.


(2Z,4E)-6-Hydroxy-3-methylhexa-2,4-dienitrile (11) (1st Method)
A mixture of iodide 1 (80 mg, 0.4146 mmol), stannyl derivative 2 (140 mg, 0.4146 mmol) and Pd(CH₃CN)₂Cl₂ (11 mg, 0.0414 mmol, 1 equiv) in THF (1.5 mL) and DMF (1.5 mL) was heated at 80 °C under argon for 2 h until all the solid had dissolved. The adduct was then cooled to 0 °C under an inert atmosphere was added a solution of CBr₄ (306 mg, 4.29 mmol, 4 equiv) in dry CH₂Cl₂ (5 mL). After 10 min, the resulting mixture was stirred for 1 h. The reaction was quenched with saturated NaHCO₃ solution, allowed to warm to r.t. over 2 h until the reaction was complete. The mixture was filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 10:1 to 1:3) to give adduct 11 as a colorless oil (20 mg, 39%).


(2Z,4E)-6-Hydroxy-3-methylhexa-2,4-dienitrile (11) (2nd Method)
The adduct 11 was also obtained by a slightly modified procedure.[32] Under argon at 0 °C, DIBAL-H (0.62 mL, 1 M in hexane, 0.62 mmol, 1.5 equiv) was added slowly via syringe to a solution of alcohol 2 (140 mg, 0.79 mmol, 1 equiv) in dry CH₂Cl₂ (1 mL) was added dropwise at the same temperature. The mixture was then allowed to warm to r.t. for 2 h until the reaction was complete, MnO₂ was removed by filtration through a pad of Celite® and the pad was rinsed with CH₂Cl₂. The filtrate was concentrated under vacuum to give 12 as a colorless oil (16 mg, 90%).

(2Z,4E)-3-Methyl-6-oxohexa-2,4-dienitrile (12) (2nd Method)
To a solution of 11 (97 mg, 0.50 mmol, 1 equiv) in MeCN (2 mL) covered with aluminum foil were added acrolein (4) (0.33 mm, 5.03 mmol, 10 equiv), Pd(OAc)₂ (6 mg, 0.025 mmol, 5 mol%) and AgOAc (100 mg, 0.60 mmol, 1.2 equiv) and reaction mixture was stirred under argon in the dark for 48 h at r.t. The mixture was filtered through a pad of SiO₂, the pad was rinsed with Et₂O and the filtrate was concentrated under vacuum. The residue was purified by column chromatography on SiO₂ (hexane/ EtOAc, 15:1 to 1:1) to give 12 (52 mg, 85%).

IR (thin film): 2217, 1682, 1132, 985, 862 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 3.47 (dd, J = 15.3, 10.4, 0.4 Hz, 1 H), 5.29 (d, J = 15.4 Hz, 1 H), 6.58 (dd, J = 15.3, 10.4, 0.4 Hz, 1 H), 5.29 (d, J = 0.5 Hz, 1 H), 2.08 (d, J = 1.2 Hz, 3 H).

13C NMR (101 MHz, CDCl₃): δ = 155.43, 136.30, 132.47, 131.87, 116.69, 98.91, 97.29, 19.28.


(2Z,4E)-7,7-Dibromo-3-methylhepta-2,4,6-trienitrile (14)
To a solution of Ph₃P (2.2 g, 8.59 mmol, 8 equiv) in dry CH₂Cl₂ (20 mL) cooled to 0 °C under an inert atmosphere was added a solution of CBr₄ (306 mg, 4.29 mmol, 4 equiv) in dry CH₂Cl₂ (5 mL). After 10 min, the mixture turned yellow and was cooled to −50 °C. A solution of aldehyde 12 (130 mg, 1.07 mmol, 1 equiv) in dry CH₂Cl₂ (1 mL) was added dropwise at the same temperature. The mixture was then allowed to warm to r.t. over 2 h until the reaction was complete. Hexane was added and the precipitate was removed by filtration. The filtrate was concentrated under vacuum and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 1:1) to give dibromide 14 (180 mg, 61%) as a white solid.

IR (thin film): 3412, 2212, 1643, 1585, 1436, 1097, 965 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.13 (dd, J = 10.4, 0.6 Hz, 1 H), 6.94 (d, J = 15.4 Hz, 1 H), 6.58 (dd, J = 15.3, 10.4, 0.4 Hz, 1 H), 5.29 (d, J = 0.5 Hz, 1 H), 2.08 (d, J = 1.2 Hz, 3 H).

13C NMR (101 MHz, CDCl₃): δ = 155.43, 136.30, 132.47, 131.87, 116.69, 98.91, 97.29, 19.28.


(3-E)-tert-Butyl[(3-iodobut-2-en-1-yl)oxy]dimethylsilane (15)
To a solution of iodide 11 (156 mg, 0.79 mmol, 1 equiv) in dry CH₂Cl₂ (3 mL) at −78 °C were added dropwise t-Bu₂Me₂SiO (0.27 mL, 1.18 mmol, 1.5 equiv) and 2,6-lutidine (0.27 mL, 1.18 mmol, 3 equiv) and the resulting mixture was stirred for 1 h. The reaction was quenched with saturated NaHCO₃ solution, allowed to warm to r.t. and extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 30:1 to 1:1) to give 15 (236 mg, 96%) as a colorless oil.


1H NMR (400 MHz, CDCl₃): δ = 5.35 (s, J = 15.6, 1 H), 4.12 (ddd, J = 6.5, 1.8, 0.8 Hz, 2 H), 2.41 (dt, J = 1.6, 0.9 Hz, 3 H), 0.90 (s, 9 H), 0.07 (s, 6 H).

13C NMR (101 MHz, CDCl₃): δ = 140.80, 138.21, 138.21, 136.21, 136.21, 134.39, 134.39, 132.47, 131.87, 116.69, 98.91, 97.29, 19.28.

The data are consistent with those reported in the literature.[51]

(2Z)-3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-en-1-ol (16)

The product 16 (0.5 g, 69% yield) was obtained from 2-butyn-1-ol (6) (253 mg, 3.58 mmol) according to the literature procedure.[46]

(2Z,4E,6Z,8E)-7-Bromo-10-hydroxy-3,8-dimethyledeca-2,4,6,8-tetraenerrinitile (17)

To a solution of 16 (56 mg, 0.28 mmol, 1 equiv) in degassed THF (0.45 mL) under an argon atmosphere was added TIOEt (0.018 mL, 0.25 mmol, 1 equiv) followed by H2O (0.04 mL) and the resulting mixture was stirred at r.t. for 5 min. A solution of 17 (70 mg, 0.25 mmol, 1 equiv) and Pd(PPh3)4 (15 mg, 0.013 mmol, 0.05 equiv) in THF (1 mL) was added and the mixture was stirred at r.t. for 4 h. After filtration through a pad of Celite® and Na2SO4, the filtrate was concentrated under vacuum and the residue purified by column chromatography on SiO2 (hexane/Et2O, 100:1 to 35:1) to give tetraenenritile (20) (32 mg, 31%), and (2) adduct 17 (43 mg, 63%), which was isolated crude and used in the next step without purification.

(2Z,4E,6Z,8E)-7-Bromo-10-[( tert-butyldimethylsilyloxy)-3,8-dimethyledeca-2,4,6,8-tetraenerrinitile (18) and (2Z,4Z,6E)-6-Bromo-8-[( tert-butyldimethylsilyloxy) methyl]-2,7-dimethylcycloocta-2,6,8-triene-1-carbonitrile (19)

A solution of 17 (40 mg, 0.15 mmol, 1 equiv) in CH2Cl2 (1.5 mL) was cooled to ~85 °C under an argon atmosphere and 2.6-lutidine (0.05 mL, 0.45 mmol, 3 equiv) was added, followed by the addition of tert-BuMe2SiOTf (0.05 mL, 0.22 mmol, 1.5 equiv). The mixture was stirred at this temperature for 1 h and then quenched by the addition of brine. The mixture was allowed to warm to r.t. and then extracted with Et2O, dried over Na2SO4 and concentrated under vacuum. The residue was purified by column chromatography on SiO2 (hexane/Et2O, 100:1 to 35:1) to give tetraenanitrile 18 (52 mg, 91%) and cyclized compound 19 (5 mg, 8%).

Compound 18

IR (thin film): 2954, 2929, 2885, 2856, 2209, 1595, 1253, 1105, 1070, 834, 769 cm–1.

1H NMR (400 MHz, CDCl3): δ = 6.99 (dd, J = 15.0, 11.0 Hz, 1 H), 6.85 (d, J = 15.0 Hz, 1 H), 6.38 (d, J = 11.0 Hz, 1 H), 5.86 (d, J = 5.6 Hz, 1 H), 5.09 (s, 1 H), 4.40 (d, J = 5.8 Hz, 2 H), 2.07 (d, J = 1.3 Hz, 3 H), 2.02 (s, 3 H), 1.84 (d, J = 0.8 Hz, 3 H), 0.92 (s, 9 H), 0.09 (s, 6 H).

13C NMR (101 MHz, CDCl3): δ = 156.64, 143.16, 135.98, 133.59, 130.57, 129.45, 125.30, 117.50, 95.44, 61.43, 26.13, 19.37, 18.56, 14.69, 14.31, –4.95.


(E)-3-Iodobut-2-en-1-ol (21)

Under argon at 0 °C, DIBAL-H (4.28 mL, 1 M in hexane, 4.28 mmol, 1 equiv) was added slowly via syringe to a solution of but-2-yn-1-ol (6) (300 mg, 4.28 mmol, 1 equiv) in THF (0.3 mL) and the solution was then allowed to warm to r.t. and stirred for 1 h. To another flask covered with aluminum foil under argon were added Cp2ZrCl2 (2.5 g, 8.56 mmol, 2 equiv) and THF (15 mL). To this suspension was added dropwise DIBAL-H (8.6 mL, 1 M in hexane, 8.6 mmol, 2 equiv) at 0 °C. After 30 min, the pretreated alcohol mixture was transferred via cannula into the second reaction flask and the resulting mixture was stirred at 40 °C for 3.5 h until all the solid had dissolved. Next, the mixture was cooled to 0 °C and treated with a solution of I2 (2.4 g, 9.42 mmol, 2.2 equiv) in THF (5 mL). After stirring at 0 °C for 15 min, the mixture was diluted with Et2O and quenched with saturated Na2SO4 solution. The mixture was extracted with Et2O and the combined organic layers were dried over Na2SO4 and concentrated under reduced pressure. The residue was purified by column chromatography on SiO2 (hexane/Et2O, 40:1 to 3:1) to give 21 (402 mg, 47%).

1H NMR (400 MHz, CDCl3): δ = 6.44–6.38 (m, 1 H), 4.09 (t, J = 6.0 Hz, 2 H), 2.45 (d, J = 0.7 Hz, 3 H), 1.46 (br s, 1 H).

13C NMR (101 MHz, CDCl3): δ = 139.85, 98.71, 60.10, 28.16.

The data are consistent with those reported in the literature.[52]

3-Hydroxy-2-methylpentanal (24)

The product was obtained by the 4-trans-hydroxy-l-proline-catalyzed aldol reaction of propionaldehyde in DMSO at 4 °C.[40]

3-[( tert-Butyldimethylsilyloxy)-2-methylpentanal (25)

To a solution of aldehyde 24 (0.5 g, 4.3 mmol) and DIPEA (3.2 mL, 18.4 mmol) in dry CH2Cl2 (20 mL) cooled to ~5 °C was added t-BuMe2SiOTf (3 mL, 13.1 mmol) dropwise and stirring was continued for 1 h. During this time the temperature rose to 0 °C, and at this point the reaction was quenched with saturated NaHCO3 solution and extracted
with CH2Cl2. The combined organic fractions were dried over Na2SO4, filtered, and concentrated under reduced pressure without heating. The residue was purified by column chromatography on silica gel (hexane/EtO, 40:1 to 16:1) to give 25 (0.97 g, 98%) as a colorless oil.

IR (thin film): 2958, 2931, 2858, 1726, 1463, 1253, 833, 773, 668 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 9.74 (dd, J = 7.3, 1.7 Hz, 1 H), 4.02 (dd, J = 6.6, 3.7 Hz, 0.5 H), 3.85 (J = 5.5 Hz, 0.5 H), 2.55–2.40 (m, 1 H), 1.78–1.42 (m, 2 H), 1.05 (d, J = 7.0 Hz, 1.5 H), 1.04 (d, J = 6.9 Hz, 1.5 H), 0.92–0.87 (m, 3 H), 0.86 (s, 4.5 H), 0.85 (s, 4.5 H), 0.05 (s, 3 H), 0.04 (s, 3 H), 0.02 (s, 1.5 H).

13C NMR (101 MHz, CDCl3): 26.05, 18.25, 15.97, 10.01, –4.06, –4.38.

anti-26

IR (thin film): 2958, 2930, 2857, 1461, 1255, 1109, 1079, 1038, 872, 834, 773 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 6.37 (d, J = 9.5 Hz, 1 H), 3.49 (dd, J = 6.7, 5.8, 3.5 Hz, 1 H), 2.61 (m, 1 H), 1.51–1.31 (m, 2 H), 1.01 (d, J = 6.9 Hz, 3 H), 0.90 (s, 9 H), 0.87 (t, J = 7.5 Hz, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H).

13C NMR (101 MHz, CDCl3): δ = 140.96, 88.04, 76.27, 42.86, 28.14, 26.05, 18.25, 15.97, 10.01, –4.06, –4.38.


syn-27

IR (thin film): 2957, 2929, 2857, 1462, 1277, 1255, 1014, 873, 833, 773.

1H NMR (400 MHz, CDCl3): δ = 6.32 (d, J = 9.5 Hz, 1 H), 3.56 (dd, J = 11.1, 5.5 Hz, 1 H), 2.64–2.49 (m, 1 H), 1.58–1.37 (m, 2 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.90 (s, 9 H), 0.88 (s, 3 H), 0.05 (s, 3 H), 0.05 (s, 3 H).

13C NMR (101 MHz, CDCl3): δ = 142.65, 87.58, 75.45, 42.37, 27.64, 26.03, 18.27, 13.25, 9.63, –4.09, –4.50.

HRMS (ESI): m/z [M + Na]⁺ calcd for C14H28ONaSi: 263.1807; found: 263.1795.

tert-Butyldimethyl(35,4,5-4-methylhept-5-yn-3-yl)oxydimethylsilane (29)

Under argon at 0 °C, DIBAL-H (0.07 mL, 1 M in cyclohexane, 0.07 mmol, 0.3 equiv) was added slowly via syringe to a solution of 28 (60 mg, 0.25 mmol, 1 equiv) in THF (1 mL). The solution was allowed to warm to r.t. and then stirred for 1 h. To this flask covered with aluminu foil under argon were added Cp2ZrCl2 (182 mg, 0.62 mmol, 2.5 equiv) and THF (1.5 mL). To this suspension was added dropwise DIBAL-H (0.62 mL, 1 M in cyclohexane, 0.62 mmol, 2.5 equiv) at 0 °C. After 50 min, the pretreated solution of 28 was transferred via cannula into the second reaction flask, the cooling bath was removed and the mixture was allowed to warm to r.t. and then stirred at 40 °C for 1 h until all the solid had dissolved. The mixture was cooled to ~78 °C and treated with a solution of I2 (158 mg, 0.62 mmol, 2.5 equiv) in THF (1 mL) until the iodine color was present. After 5 min, the cooling bath was removed, and the mixture was allowed to warm to r.t. and then quenched with a minimum amount of aqueous Na2SO3 solution, dried over Na2SO4 and filtered through a Celit® pad. The pad was rinsed with EtO and the filtrate was concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane) to give 29 (60 mg, 65%) as a colorless oil.

IR (thin film): 2958, 2930, 2857, 1726, 1251, 1023, 1005, 832, 772 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 6.07 (d, J = 10.0 Hz, 1 H), 3.37–3.45 (m, 1 H), 2.57–2.46 (m, 1 H), 2.38 (d, J = 1.4 Hz, 3 H), 1.50–1.37 (m, 2 H), 0.94 (d, J = 6.9 Hz, 3 H), 0.89 (s, 9 H), 0.84 (t, J = 7.4 Hz, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H).

13C NMR (101 MHz, CDCl3): δ = 144.09, 93.64, 76.49, 40.12, 28.01, 27.28, 26.06, 18.24, 16.60, 9.61, –4.15, –4.26.


(2E,4E,5R,7S)-7-[(tert-Butyldimethylsilyloxy)-3,4,6-trimethylhexa-2,4-di-en-1-ol (38)

To a solution of boronic ether 16 (163 mg, 0.81 mmol, 2 equiv) in THF (1.5 mL) under argon was added TlOEt (0.05 mL, 0.73 mmol, 1.8 equiv) and degassed H2O (0.15 mL) at r.t. and the resulting mixture was stirred for 5 min. To this mixture were added a solution of iodide 29 (150 mg, 0.41 mmol, 1 equiv) in THF (0.6 mL) and Pd(PPh3)4 (23 mg, 0.02 mmol, 0.05 equiv) and stirring was continued for 4 h. The mixture was filtered through Celit® and the pad rinsed with EtO.
The filtrate was concentrated under vacuum and the residue purified by column chromatography on silica gel (hexane/EtO, 30:1 to 6:1) to give adduct 38 (161 mg, 95%) as a colorless oil.

IR (thin film): 3314, 2927, 2928, 2857, 1462, 1377, 1254, 1102, 1073, 1060, 1006, 835, 773 cm⁻¹.

1H NMR (400 MHz, CDCl₃; δ) = 5.70 (t, J = 6.3 Hz, 1 H), 5.59 (d, J = 9.5 Hz, 1 H), 4.31 (t, J = 6.0 Hz, 2 H), 3.47 (td, J = 6.1, 3.9 Hz, 1 H), 2.64 (ddq, J = 13.6, 6.8, 3.9 Hz, 1 H), 1.83 (s, 3 H), 1.81 (d, J = 1.1 Hz, 3 H), 1.32–1.50 (m, 2 H), 1.22 (t, J = 5.5 Hz, 1 H), 0.97 (d, J = 6.9 Hz, 3 H), 0.90 (s, 9 H), 0.84 (t, J = 7.4 Hz, 3 H), 0.04 (s, 6 H).

13C NMR (101 MHz, CDCl₃; δ) = 139.64, 135.02, 130.75, 124.05, 77.36, 60.29, 37.74, 27.24, 26.07, 18.28, 16.98, 14.40, 14.27, 10.27, −4.09, −4.32.


(2Z,4E,6Z,7S)-7-[(tert-Butyldimethylsilyloxy)-3,4,6-trimethyleno-2,4-dien-1]-yl bromide (39)

To a solution of alcohol 38 (96 mg, 0.31 mmol) in CH₂Cl₂ (15 ml) was added MnO₂ (0.5 g, 6.15 mmol, 20 equiv) portionwise. The reaction was complete after stirring at r.t. for 1 h. When MnO₂ was removed by filtration through a pad of Celite® and the pad was rinsed with CH₂Cl₂, the filtrate was concentrated under reduced pressure and the obtained aldehyde 39 (91 mg, 96%) was used in the next step without purification.

IR (thin film): 2957, 2927, 2857, 1606, 1379, 1350, 1257, 1143, 850 cm⁻¹.

1H NMR (400 MHz, CDCl₃; δ) = 7.43 (dd, J = 17.3, 11.0 Hz, 1 H), 6.24 (d, J = 10.9 Hz, 1 H), 5.71 (d, J = 9.0 Hz, 1 H), 5.56 (d, J = 17.3 Hz, 1 H), 3.48 (td, J = 5.9, 4.1 Hz, 1 H), 2.67 (dqd, J = 13.6, 6.8, 4.1 Hz, 1 H), 1.99 (d, J = 0.6 Hz, 3 H), 1.83 (d, J = 1.0 Hz, 3 H), 1.41 (m, 2 H), 1.28 (s, 12 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.89 (s, 9 H), 0.84 (t, J = 7.4 Hz, 3 H), 0.04 (s, 6 H).

13C NMR (101 MHz, CDCl₃; δ) = 146.75, 142.34, 135.50, 132.72, 127.13, 83.20, 77.32, 38.00, 27.25, 26.06, 24.92, 18.27, 16.92, 14.81, 14.41, 10.16, −4.10, −4.32.


(2Z,4E,6E,8E,10R,11S)-11-[(t-Butyldimethylsilyloxy)-3,7,8,10-tetrahydropyridine-2,4,6,8-tetraenemine (41)

To a solution of boronic ester 45 (27 mg, 0.06 mmol, 1 equiv) in THF (0.9 ml) under argon was added TIOEt (0.01 ml, 0.14 mmol, 2.3 equiv) and degassed H₂O (0.09 ml) at r.t. and the mixture stirred for 5 min. Next, a solution of iodide 1 (16 mg, 0.08 mmol, 1.4 equiv) in THF (1 ml) and Pd[PPh₃]₄ (7 mg, 0.006 mmol, 0.1 equiv) were added and stirring was continued for 1 h. The reaction mixture was filtered through Celite® and the pad was rinsed with EtO. The filtrate was concentrated under reduced vacuum. The residue was purified by column chromatography on silica gel (hexane/EtO, 1:1 to 8:1) to give adduct 41 (15 mg, 67%) as a colorless oil.

IR (thin film): 2957, 2929, 2856, 2209, 1591, 1378, 1360, 1252, 1078, 1029, 961, 835, 773 cm⁻¹.

1H NMR (400 MHz, CDCl₃; δ) = 7.00 (dd, J = 15.0, 11.1 Hz, 1 H), 6.84 (d, J = 15.0 Hz, 1 H), 6.35 (d, J = 11.1 Hz, 1 H), 5.79 (d, J = 9.5 Hz, 1 H), 5.07 (s, 1 H), 3.50 (td, J = 6.0, 3.9 Hz, 1 H), 2.69 (dqd, J = 13.6, 6.8, 3.9 Hz, 1 H), 2.07 (d, J = 1.3 Hz, 3 H), 2.00 (s, 3 H), 1.87 (d, J = 1.0 Hz, 3 H), 1.33–1.51 (m, 2 H), 0.99 (d, J = 6.8 Hz, 3 H), 0.90 (s, 9 H), 0.85 (t, J = 7.4 Hz, 3 H), 0.05 (s, 6 H).

13C NMR (101 MHz, CDCl₃; δ) = 156.82, 144.25, 135.41, 133.96, 133.73, 128.79, 124.49, 117.63, 94.91, 77.32, 38.02, 27.50, 26.06, 19.59, 18.28, 17.09, 14.78, 14.40, 10.13, −4.07, −4.32.


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