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Abscisic Acid Derivatives | *Very Important Paper* |

VIP

# Potent Analogues of Abscisic Acid – Identifying Cyano-Cyclopropyl Moieties as Promising Replacements for the Cyclohexenone Headgroup

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**Abstract:** Synthetic analogues of plant hormone abscisic acid (ABA) bearing a yet unexplored head group motif were prepared based on a combination of agrochemical experience, in vivo hits and structure-based design. It could thus be explored how modifying key parts of ABA's cyclohexenone unit influenced receptor affinity and in vivo efficacy against drought stress in selected crops. Cyano-cyclopropyl groups proved to be suitable replacements of the cyclohexanone moiety leading to ABA analogues with strong activity in vitro and in vivo. Their efficient and versatile synthesis proceeded via Stille or Sonogashira couplings as the key steps. Combining novel cyano-cyclopropyl headgroups with previously identified substituents in the terpenoid side chain afforded the most promising effects against drought stress in crops, particularly canola and wheat.

## Introduction

Abscisic acid [**1**, *S*-(+)-ABA], a chiral sesquiterpenoid first discovered in the 1960s,[1] is one the most important plant hormones regulating developmental signals in plants such as seed maturation or dormancy. It has been commercialized, e.g. for enhancing color development in red-table grapes. Furthermore, it mediates the adaptation of plants to environmental abiotic stress such as drought, heat or salinity stress. Several strategies have been investigated for reducing the impact of drought on yield, such as exploiting beneficial effects of crop protection agents,[2] developing drought tolerant crops through transgenic approaches or breeding,[3] but also exploring novel chemical entities inspired by naturally occurring plant hormones. Studies on ABA-mediated signaling have progressed rapidly since the recent discovery of RCAR/(PYR/PYL) receptor proteins as soluble ABA-receptors.[4] It was shown via crystal structural analysis that binding of ABA to RCAR12 induced a conformational change in the highly conserved ABA receptor proteins giving rise to an interaction with phosphoprotein phosphatases 2C (PP2Cs) thereby inhibiting their activity. Hence, these findings have granted new insights into the structure activity relationship (SAR) of ABA, whilst its catabolism had been well explored prior to identifying the RCAR/(PYR/PYL) receptor proteins. ABA's principal pathway of oxidation is through monooxygenase-mediated hydroxylation, i.e. by the CYP707A-family, of the 8′-methyl group affording 8′-hydroxy-ABA, which is in equilibrium with the cyclized form phaseic acid.[5] Thus, most chemical modifications of ABA were dedicated to stabilizing its cyclohexenone headgroup. It has been shown that metabolism-resistant analogues altered at the C8′ position were more stable towards

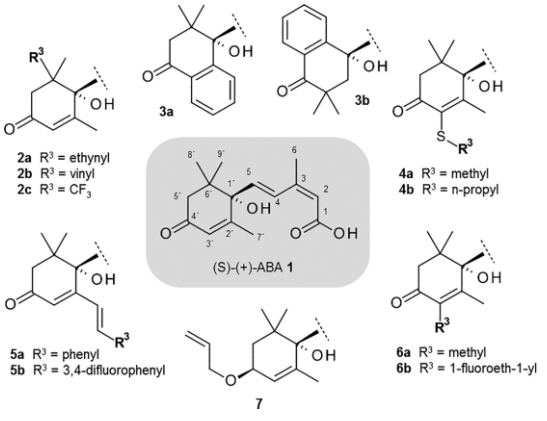


Figure 1. The structure of (*S*)-(+)-abscisic acid (**1**) with formal atom numbering and selected closely related analogues with modified headgroup.

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oxidation than ABA itself with 8′-ethynyl-ABA **2a**, 8-vinyl-ABA **2b** and 8′-trifluoromethyl-ABA **2c** exhibiting promising activity in in vitro tests.[6]

Furthermore, tetralone analogues **3a**–**b** of ABA have been prepared,[7] as well as 3′-sulfanyl-ABA analogues **4a**–**b**,[8] ABA-analogues with modified 7′-Me group **5a**–**b**[9] 3-methyl- and 3′-haloalkyl-ABA **6a**–**b**[10] or cyclohexenol **7** (Figure 1).[11] Although stabilizing or further substituting the cyclohexenone moiety has attracted significant interest, surprisingly few approaches have been made to identify open-chain analogues of ABA with promising target affinity. The first synthetic compounds interacting with RCAR/(PYR/PYL) receptor proteins have been recently prepared.[12] In our view this indicates that we can identify ABA analogues with more profound structural changes that exhibit good receptor binding and promising in vivo efficacy. Substituted aryl sulfonamides, e.g. pyrabactin **8a**,[13] closely related pyrimidine **8b**, as well as thiazoles and pyrazoles **9a**–**b**,[14] have shown promising initial receptor affinity and beneficial effects within in vivo tests (Figure 2). More recently, tetrahydroquinolinyl sulfonamides have shown improved in vitro activity.[15] Interestingly, it was demonstrated further that the sulfonamide unit in these hit structures could be replaced by phosphonamides preserving binding affinity and thus emphasizing opportunities to introduce further structural motifs into ABA-related structures.[16] Herein, we outline how we identified unprecedented potent analogues of ABA carrying cyano-cyclopropyl moieties as replacements of its cyclohexenone headgroup, and we discuss the structural basis of their beneficial effects against drought stress observed in the course of our in vivo-studies.

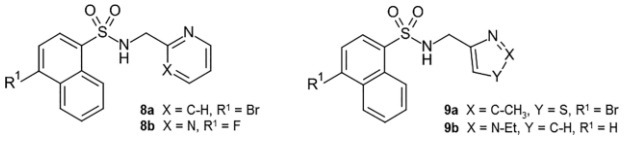



Figure 2. Selected naphthyl sulfonamides interacting with RCAR/(PYR/PYL) receptor proteins.

## Results and Discussion

### Hit Exploration, Modeling and X-ray Studies

Inspired by structural features from earlier agrochemical projects (e.g. **10**) and from in vivo hits **11**, **12** showing promising efficacy against drought stress (Figure 3)[17] we have initiated modeling studies to identify novel head group motifs with good binding affinity to the ABA-receptors.

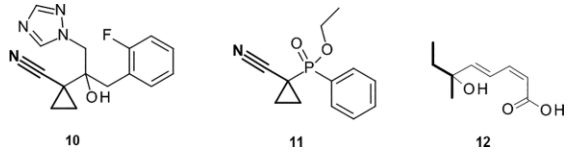



Figure 3. In vivo hit structures with interesting structural motifs.

As a starting point, compound **11** was docked initially into the ABA binding site of the published crystal structure of ABA-bound RCAR12 and related phosphatase ABI1 (PDB: 3 KDJ) since complex structures of RCAR11 with bound ABA and HAB1 were not available at that time. Resulting poses were then scored using the HYDE scoring function[18,19] with the best ranked pose having an energy of –41 kJ/mol corresponding to a binding affinity in micromolar range (Figure 4a, **11** superimposed with ABA). The quaternary phosphorus atom of **11** is located at the position of the quaternary carbon of ABA, while the P=O moiety replaces the hydroxyl function of ABA forming the same H-bond to a water molecule at the protein ligand interface. Furthermore, the nitrile moiety of **11** forms an H-bond to the water molecule at the interface between RCAR12 and HAB1 adopting the role of the carbonyl oxygen in ABA. This conserved water molecule forms all four possible H-bonds including H-bonds to the backbone oxygen of proline 115 and backbone amide of arginine 143 from RCAR12 and NE1 of tryptophan 300 from ABI1. It thus represents a key element in the protein–protein interaction between the RCARs and the corresponding phosphatases. Interestingly, the nitrile nitrogen and the carbonyl oxygen are not located at the same place due to different localizations of the free electron pair serving as the H-bond donor. The binding mode of **11** was subsequently confirmed by a co-crystal structure with the closely homologous ABA receptor RCAR11 and the phosphatase HAB1 (Figure 4b).

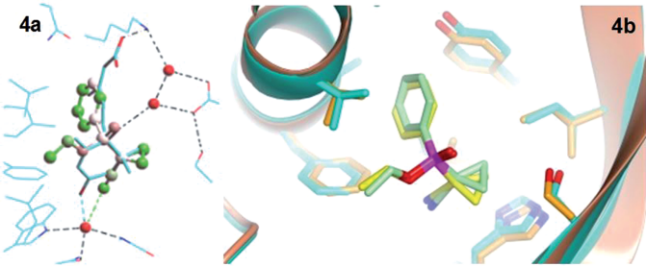



Figure 4. (a) Superposition of the best ranked docking pose of **11** with ABA bound to RCAR12 and ABI1. The color code of **11** indicates the stabilization of individual atoms ranging from –3 kJ/mol (dark green) to +3 kJ/mol (dark red). Common H-bonds are marked in black while the H-bond to the conserved water molecule is cyan in case of ABA and green in case of **11**. (b) Superposition of the docking model of **11** (green) in the ABA binding site of RCAR12/ABI1 (cyan) with the crystal structure of **11** (yellow) in complex with RCAR11/HAB1 (orange).

Visual inspection of ABA's superposition and the predicted binding mode of **11** suggested a chemical entity **16a** combining the diene moiety of ABA with the cyano-cyclopropyl moiety of **11**. The crystal structure of **16a** bound to RCAR11 and HAB1 proved its potential to mimic the binding mode of ABA thus representing an excellent novel synthetic analogue of natural product ABA (Figure 5). In particular, all H-bonds are conserved in the crystal structure of **16a** bound to RCAR11 and HAB1 including the H-bond to the conserved water molecule that bridges tryptophan 385 and the backbone of RCAR11 (Figure 5). Similar to the binding of ABA, space for hydrophobic substituents of a limited size was identified at position $R^2$, and further analysis of the X-ray structure also indicated space for introducing hydrophobic groups at position $R^1$. These findings prompted us to start a broad SAR study.

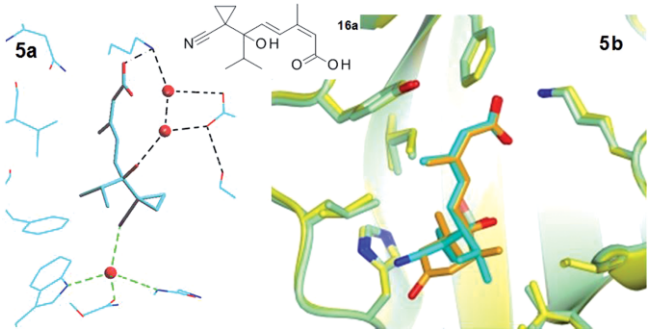
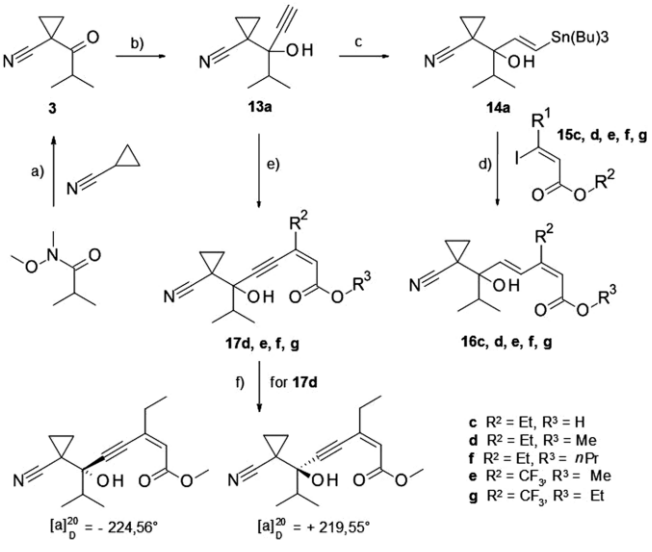



Figure 5. (a) Details of molecular interaction of **16a** bound to RCAR11 and HAB1. H-bonds are marked in black except for those to the conserved water molecule which are marked in green. b) Comparison of RCAR11/HAB1 complex structures of **16a** (ligand in cyan, protein in green) and ABA (ligand in orange, protein in yellow).

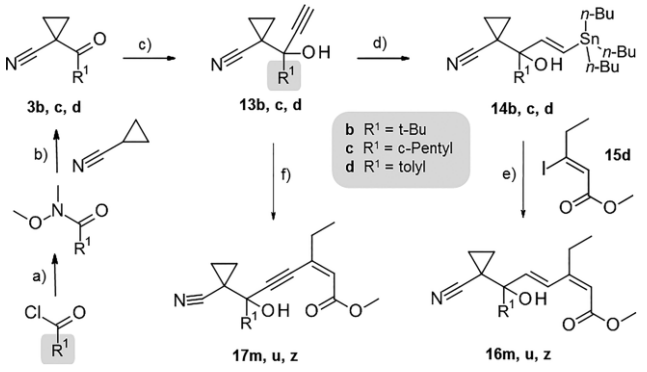
## Chemistry

Based on our experiences from total synthesis studies in the field of ABA we decided to apply our versatile approach using a Stille coupling as the key step to prepare cyano-cyclopropyl analogues of ABA.[20] LDA-mediated coupling of cyclopropyl nitrile with a pivaloyl-based Weinreb amide, followed by direct alkynylation afforded crystalline alkynol **13a** in good yield (Scheme 1). Subsequently, **13a** could then be easily transformed selectively into (*E*)-configured key intermediate **14a** via $Pd(PPh_3)_2Cl_2$-mediated hydrostannylation.



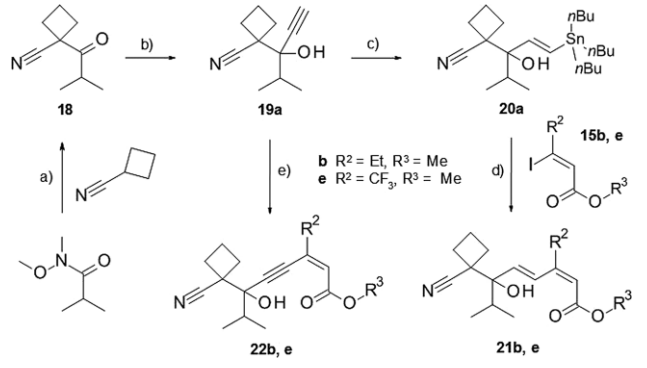

Scheme 1. Cross-coupling-mediated synthesis of cyano cyclopropyl analogues of ABA with $R^1$ = *i*Pr. a) lithium diisopropylamide (LDA), THF, –78° to room temp., 5 h; b) Li-acetylide ethylene diamine complex, THF, r.t.; c) $Bu_3SnH$, $Pd(PPh_3)_2Cl_2$, THF, r.t.; d) **15c**, **d, e**, **f** or **g**, $Pd(MeCN)_2Cl_2$, CuI, DMF, 50 °C; e) $Pd(PPh_3)_2Cl_2$, CuI, diisopropylamine, toluene, r.t.; f) chiral prep. HPLC.

Coupling of (*E*)-stannane **14a** with a suitable freshly prepared vinyl iodide **15c**–**15g** via an optimized Stille-coupling protocol using $Pd(MeCN)_2Cl_2$ and CuI in *N*,*N*-DMF at slightly elevated temperatures (40–50 °C) afforded desired cyano-cyclopropyl analogues of ABA **16c**–**16g**.[22] (*Z*)-Vinyl iodides **15c**–**15g** were prepared starting from substituted alkynes in two steps via carboxylation and subsequent hydroiodination.[21] In our hands, this methodology proved to be clearly superior towards related approaches using hydrozirconation and a Negishi-type cross-coupling to establish the (*E*,*Z*)-diene side chain.[22] As a result, ABA-analogues **16c**–**16g** could be prepared in 5 linear steps with overall yields in the range of 30–50 % (Scheme 1). Alkynol **13a** also served as a key intermediate to prepare related enynes **17d**–**g** via Sonogashira coupling. Enyne **17d** could be separated into both enantiomers via prep. HPLC. Interestingly, both enantiomers showed comparable in vitro and in vivo activity prompting us to use racemates in our SAR study. With this robust synthetic approach in hand we could prepare a broad range of compounds with modified head groups (Scheme 2; entries 2–27, Table 1). The *i*Pr group ($R^1$) could thus be replaced by a wide variety of alkyl, cycloalkyl and aryl substituents, such as cyclopropyl, cyclopentyl, *tert*-butyl, adamantyl, phenyl or tolyl, emphasizing the versatility of our synthetic approach (**16m**, **16u**, **16z**, Scheme 2, Table 1, Table 2).[22]




Scheme 2. Cross-coupling-mediated synthesis of cyano cyclopropyl analogues of ABA with various substituents $R^1$. a) MeO-NHMe, $NaHCO_3$, THF; b) LDA, THF, –78 °C to r.t, 5 h; c) Li-acetylide ethylene diamine complex, THF, room temp.; d) $Bu_3SnH$, $Pd(PPh_3)_2Cl_2$, THF, r.t.; e) **15d**, $Pd(MeCN)_2Cl_2$, CuI, DMF, 50 °C; f) $Pd(PPh_3)_2Cl_2$, CuI, diisopropylamine, toluene, r.t.

To broaden our SAR study further we aimed to enlarge the ring size of the cyano-cycloalkyl unit. Having chosen the cyano-cyclobutyl moiety as a representative motif, we applied our synthetic approach outlined in Scheme 1 and Scheme 2 to cyclobutyl nitrile (Scheme 3) affording (*E*)-stannane **20a** and desired




Scheme 3. Cross-coupling-mediated synthesis of cyano cyclobutyl analogues of ABA with $R^1$ = *i*Pr. a) LDA, THF, –78 °C to room temp., 5 h; b) Li-acetylide ethylene diamine complex, THF, r.t.; c) $Bu_3SnH$, $Pd(PPh_3)_2Cl_2$, THF, r.t.; d) **15b**, **e**, $Pd(MeCN)_2Cl_2$, CuI, DMF, 50 °C; e) $Pd(PPh_3)_2Cl_2$, CuI, diisopropylamine, toluene, r.t.

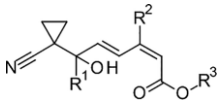
diene target compounds **21b** and **21e** in good yield. Likewise, related enynes **22b** and **22e** were obtained via Sonogashira coupling.

The utility of stannanes **14** as versatile intermediates could be demonstrated further by the preparation of cyclized analogues via Stille and Suzuki couplings. This enabled us to evaluate the impact of a cyclohexenyl or substituted phenyl group as rigid replacements for the (*Z*)-configured double bond.[23]

### In Vitro and in Vivo SAR Study

All ABA-analogues with modified headgroups were tested both, for target affinity, as well as for beneficial effects in vivo under drought stress conditions upon foliar application on plants. Wheat and Canola were chosen as model plants for mono-cotyledonous and dicotyledonous species, whereas in vitro tests were carried out at the ABA-receptor system RCAR11 in *Arabidopsis thaliana*. Based on experiences regarding herbicidal antidotes being used as Safeners[24] we also laid emphasis on exploring the impact of esters on in vivo efficacy. In contrast to conclusions from earlier studies, good receptor affinity as well as promising efficacy against drought stress in vivo could be observed for ABA-derivatives containing both, modified non-cyclic headgroups and a diene side chain with modified substituents at C6.

Table 1. SAR-results of selected cyano cyclopropyl diene-analogues of ABA.



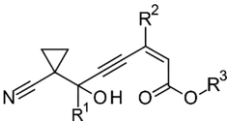

| | | Substituents[a] | | | In vitro activity ABI1-(AtRCAR11)[b] | | In vivo efficacy vs. drought stress [250 g/ha][c] | |
|---|---|---|---|---|---|---|---|---|
| Entry | No. | $R^1$ | $R^2$ | $R^3$ | Activity [%] 5 µM | $pI_{50}$ | Wheat[c] | Canola[c] |
| 1 | **1** | [e] | Me | H | 100 | 7.1 | +++[d] | +++ |
| 2 | **16a** | *i*Pr | Me | H | 100 | 5.9 | ++++ | ++++ |
| 3 | **16b** | *i*Pr | Me | Et | 99[b] | 5.9[b] | ++++ | +++ |
| 4 | **16c** | *i*Pr | Et | H | 100 | 6.1 | +++ | ++++ |
| 5 | **16d** | *i*Pr | Et | Me | 95[b] | 5.8[b] | ++++ | +++ |
| 6 | **16e** | *i*Pr | $CF_3$ | Me | 94[b] | 5.8[b] | +++ | +++ |
| 7 | **16f** | *i*Pr | Et | *n*Pr | 94[b] | 6.0[b] | ++++ | +++ |
| 8 | **16g** | *i*Pr | $CF_3$ | Et | 99[b] | 5.9[b] | +++ | +++ |
| 9 | **16h** | *i*Pr | $CF_3$ | *n*Pr | 99[b] | 5.9[b] | +++ | +++ |
| 10 | **16i** | *i*Pr | *c*Pent | Et | 72[b] | 4.3[b] | + | + |
| 11 | **16j** | *t*Bu | Me | Et | 95[b] | 6.1[b] | +++ | ++ |
| 12 | **16k** | *t*Bu | $CF_3$ | Me | 96[b] | 6.1[b] | ++ | ++ |
| 13 | **16l** | *t*Bu | $CF_3$ | Et | 94[b] | 6.2[b] | ++ | ++ |
| 14 | **16m** | *t*Bu | Et | Me | 98[b] | 6.1[b] | +++ | ++ |
| 15 | **16n** | *i*Pent | Me | Et | 100[b] | 5.9[b] | + | +++ |
| 16 | **16o** | *i*Pent | $CF_3$ | Me | 99[b] | 5.9[b] | + | ++ |
| 17 | **16p** | *i*Pent | $CF_3$ | *n*Pr | 99[b] | 5.9[b] | + | ++ |
| 18 | **16q** | *i*Pent | Et | Me | 100[b] | 6.1[b] | + | ++ |
| 19 | **16r** | *c*Pr | $CF_3$ | Me | 100[b] | 6.1[b] | +++ | ++++ |
| 20 | **16s** | *c*Pent | $CF_3$ | Me | 95[b] | 6.3[b] | + | ++ |
| 21 | **16t** | *c*Pent | $CF_3$ | Et | 95[b] | 6.1[b] | + | + |
| 22 | **16u** | *c*Pent | Et | Me | 95[b] | 6.3[b] | + | ++ |
| 23 | **16v** | *c*Hex | Me | Et | 100[b] | 6.0[b] | + | +++ |
| 24 | **16w** | *c*Hex | $CF_3$ | Me | 97[b] | 5.8[b] | + | ++ |
| 25 | **16x** | *c*Hex | Et | Me | 100[b] | 6.1[b] | + | ++ |
| 26 | **16y** | tolyl | Me | Et | 84[b] | 5.1[b] | + | + |
| 27 | **16z** | tolyl | Et | Me | 94[b] | 5.4[b] | + | + |

[a] *c*Pr = cyclopropyl, *t*Bu = 1,1-dimethyl-eth-1-yl, *c*Pent = cyclopentyl, *i*Pent = 1-ethylprop-1-yl, *c*Hex = cyclohexyl, tolyl = *p*-$CH_3$–$C_6H_4$. [b] Target affinity of esters was measured after addition of pig liver esterase. [c] Standard application rate for crop protection greenhouse trials. [d] A final expert assessment of efficacies was made according to the following classification: "0" = no effect, "+" = slight beneficial effect, "++" = significant beneficial effect, "+++" = strong beneficial effect against drought stress, "++++" = very strong effect superior to internal standard ABA (comparative visual assessment of greenmass). [e] Cyclic cyclohexanone headgroup of ABA.

Firstly, good and consistent binding affinity to RCAR11 was observed for all ABA analogues bearing cyano cyclopropyl headgroups with isopropyl [**16a**–**16h** (entries 2–9, Table 1)] and cyclopropyl (**16r**, entry 19) groups at position $R^1$. These derivatives showed highly promising effects against drought stress in wheat and canola in greenhouse experiments. In line with results from earlier studies (focusing on side chain variations of ABA) binding affinity to RCAR11 and in vivo efficacy of **16i** (entry 10) dropped sharply due to the presence of a bulky cyclopentyl group at position $R^2$ in its diene side chain.[20] Hence, we introduced only the most promising groups at $R^2$, such as methyl, ethyl or trifluoromethyl, to investigate the impact of structural changes in cyano-cyclopropyl-based headgroups. Analogues with bulkier secondary substituents $R^1$, such as 1-ethylprop-1-yl (**16n**–**16q**, entries 15–18), cyclopentyl (**16s**–**u**, entries 20–22), and cyclohexyl (**16v**–**16x**, entries 23–25) showed still good receptor affinity, however, in vivo efficacy in wheat dropped significantly combined with overall weaker efficacy in canola. Whilst analogues with a quaternary *tert*-butyl substituent at $R^1$ (**16j**–**16m**, entries 11–14) were highly active in vitro combined with moderate efficacy in vivo, aromatic substituents at $R^1$ (e.g. tolyl, **16y**, **16z**, entries 25 and 26) led to a sharp loss in in vivo efficacy. Surprisingly, *tert*-butyl derviatives **16j**–**16m** consistently showed best effects in wheat rather than in canola. Likewise, cyano-cyclobutyl analogues afforded good target affinities in line with good effects in green house experiments when bearing small alkyl and cycloalkyl substituents as in compounds **21b** and **21e** (Scheme 3). However, these results were on a slightly lower level than for parent cyano-cyclopropyl compounds **16b** and **16e** (e.g. **21b**: $pI_{50}$ 5.6, wheat: +++, canola: ++). As a result, five novel ABA-analogues with cyano-cyclopropyl headgroup ($R^1$ = *i*Pr, *c*Pr) were identified exhibiting improved in vivo efficacy than ABA **1** (Entry 1, Table 1) as reference. Earlier we showed that an enyne side chain is a good mimic of the corresponding diene units of ABA analogs ensuring the same crucial interactions of cyclohexanone and carboxylate units with RCAR11.[20] To broaden our SAR study further, as well as to evaluate the impact of the (*E*)-alkene linker, we prepared a set of corresponding enynes bearing related modified substituents at positions $R^1$ and $R^2$ (**17a**–**z**, Entries 1–24, Table 2).

A similar pattern of in vitro and in vivo activity could be observed for enynes **17a**–**z**, albeit on a slightly lower level. This may reflect the lower flexibility of enynes compared to related dienes. In good accordance with results obtained for diene-analogues with isopropyl and cyclopropyl groups at position $R^1$ (Table 1) enynes **17b**, **17c** and **17d** (Entries 2, 3 and 14, Table 2)

Table 2. SAR-results of selected cyano cyclopropyl enyne-analogues of ABA.



| | | Substituents[a] | | | In vitro activity ABI1-(AtRCAR11)[b] | | In vivo efficacy vs. drought stress [250 g/ha] | |
|---|---|---|---|---|---|---|---|---|
| Entry | No. | $R^1$ | $R^2$ | $R^3$ | Activity [%] 5 μM | $pI_{50}$ | Wheat[c] | Canola[c] |
| 1 | **17a** | Me | Me | Et | 79[b] | 5.1[b] | ++ | ++ |
| 2 | **17b** | *i*Pr | Me | Et | 97[b] | 5.9[b] | ++++ | +++ |
| 3 | **17d** | *i*Pr | Et | Me | 98[b] | 5.8[b] | ++++ | ++++ |
| 4 | ***R*-17d** | *i*Pr | Et | Me | 93[b] | 5.4[b] | +++ | +++ |
| 5 | ***S*-17d** | *i*Pr | Et | Me | 99[b] | 5.9[b] | ++++ | ++++ |
| 6 | **17e** | *i*Pr | $CF_3$ | Me | 96[b] | 5.8[b] | +++ | +++ |
| 7 | **17f** | *i*Pr | Et | *n*Pr | 96[b] | 5.8[b] | +++ | +++ |
| 8 | **17g** | *i*Pr | $CF_3$ | Et | 99[b] | 5.9[b] | +++ | +++ |
| 9 | **17h** | *i*Pr | $CF_3$ | *n*Pr | 96[b] | 5.7[b] | +++ | +++ |
| 10 | **17i** | *i*Pr | *c*Pr | Et | 99[b] | 5.9[b] | ++ | +++ |
| 11 | **17n** | *i*Pent | Me | Et | 92[b] | 5.3[b] | + | ++ |
| 12 | **17o** | *i*Pent | $CF_3$ | Me | 86[b] | 5.0[b] | + | ++ |
| 13 | **17r** | *c*Pr | $CF_3$ | Me | 99[b] | 5.6[b] | ++ | +++ |
| 14 | **17c** | *c*Pr | Et | Me | 100[b] | 5.9[b] | ++ | ++++ |
| 15 | **17j** | *c*Bu | $CF_3$ | Me | 99[b] | 5.6[b] | ++ | +++ |
| 16 | **17l** | *c*Bu | Et | Me | 100[b] | 6.0[b] | ++ | ++++ |
| 17 | **17m** | *t*Bu | Et | Me | 92[b] | 5.3[b] | ++ | ++ |
| 18 | **17u** | *c*Pent | Et | Me | 94[b] | 5.2[b] | + | ++ |
| 19 | **17v** | *c*Hex | Me | Et | 93[b] | 5.1[b] | + | + |
| 20 | **17q** | Ph | Me | Et | 91[b] | 5.5[b] | +++ | ++ |
| 21 | **17s** | Ph | $CF_3$ | Me | 93[b] | 5.3[b] | ++ | ++ |
| 22 | **17x** | *p*-F-Ph | Et | Et | 88[b] | 5.4[b] | ++ | ++ |
| 23 | **17y** | tolyl | Me | Et | 84[b] | 5.1[b] | + | ++ |
| 24 | **17z** | tolyl | Et | Me | 90[b] | 5.3[b] | + | ++ |

[a] See footnote [a] in Table 1. [b] Target affinity of esters was measured after addition of pig liver esterase. [c] A final assessment of the respective efficacy was made according to the following classification: "0" = no effect, "+" = slight beneficial effect, "++" = significant beneficial effect, "+++" = strong beneficial effect against drought stress, "++++" = very strong effect superior to internal standard ABA (comp. vis. assessment of greenmass).

showed the best activities, both in vitro and in vivo. Furthermore, $R^1$ = cyclobutyl was well tolerated, exhibiting good target affinity as well as good effects in vivo against drought stress (**17j** and **17l**, entries 15 and 16, Table 2). Derivatives with bulkier branched alkyl, cycloalkyl and aryl groups gave weaker results, correlating with what we had observed for related dienes with modified $R^1$ groups. Likewise, cyano cyclobutyl-substituted enynes afforded good target affinities in line with good effects in green house experiments on a slightly lower level than related dienes when bearing small alkyl and cycloalkyl substituents as in compounds **22b** and **22e** ($pI_{50}$ 5.2, wheat: ++, canola: ++, Scheme 3).

Interestingly, both enantiomers of **17d** proved to be active in vitro and in vivo. To validate our in vivo screening results further, we selected certain ABA-analogues for advanced greenhouse trials (i.e. more replicates, additional crops such as corn and barley, different corn varieties and moderate stress levels). Accordingly, significant beneficial effects against drought stress could also be observed in corn, barley and wheat compared to untreated controls upon treatment with **16b** and **17d** as representative examples (Figure 6).

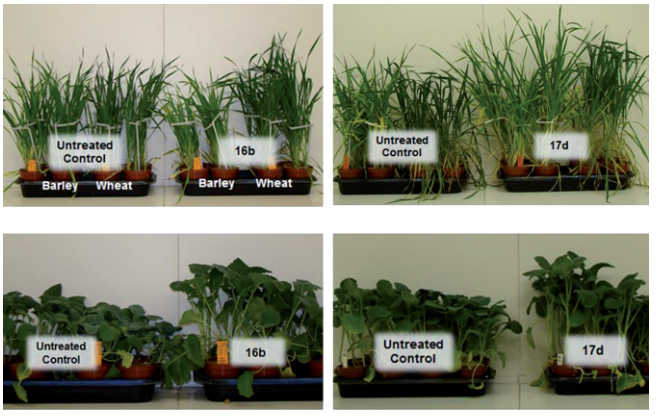



Figure 6. Advanced drought stress trials with **16b** and **17d** in wheat, barley and canola under moderate stress conditions, i.e. 45 % damage for canola, 42 % damage for barley and 48 % for wheat, respectively.

## Conclusions

We have identified a novel headgroup bearing a cyano-cyclopropyl moiety as a key motif, which proved to be a suitable replacement of ABA's cyclohexenone unit. These findings gave rise to a series of novel ABA analogues with strong activity in vitro and in vivo. Our flexible synthetic approach via cross-coupling chemistry enabled us to investigate in vivo activities of a large set of new ABA-analogues against drought stress. In total, we have identified seven highly potent analogues of ABA with improved in vivo efficacy against drought stress in canola and wheat. Results from in vitro measurements and crystal structure analyses have confirmed excellent interaction with key functionalities of the ABA-receptor emphasizing the potential of our cyano-cyclopropyl-based headgroups to act as bioisosters of cyclohexenones. The best substituents at $R^1$ were isopropyl and cyclopropyl combined with small lipophilic substituents such as $CF_3$ and ethyl at ABA's position C6 in the diene side chain. Remarkably, enynes proved to be as strong as related dienes in in vivo tests.

## Experimental Section

**Biology: In Vivo:** Seeds of monocotyledonous and dicotyledonous crop plants were laid out in sandy loam in wood-fiber pots, covered with soil and cultivated in a greenhouse under good growth conditions. The test plants were treated at the early leaf stage (BBCH10–BBCH13). To ensure uniform water supply before commencement of stress, the potted plants were supplied with the maximum amount of water immediately beforehand by dam irrigation and, after application, transferred into plastic inserts in order to prevent subsequent, excessively rapid drying. The respective compounds, formulated in the form of wettable powders (WP), wettable granules (WG), suspension concentrates (SC) or emulsion concentrates (EC), were sprayed onto the green parts of the plants as an aqueous suspension at an equivalent water application rate of 600 L/ha with addition of 0.2 % wetting agent (agrotin). Substance application is followed immediately by drought stress treatment of the plants.

Drought stress was induced by gradual drying out under the following conditions: "day" = 14 hours with illumination at 26 °C; "night" = 10 hours without illumination at 18 °C. The duration of the respective stress phases was guided mainly by the state of the untreated (treated with blank formulation but without test compound), stressed control plants and thus varied from crop to crop. It was ended (by re-irrigating or transfer to a greenhouse with good growth conditions) as soon as irreversible damage was observed on the untreated, stressed control plants. In the case of dicotyledonous crops, for example oilseed rape, the duration of the drought stress phase varied between 3 and 5 days; in the case of monocotyledonous crops, for example wheat, it varied between 6 and 10 days. The end of the stress phase was followed by an approx. 5–7-day recovery phase, during which the plants were once again kept under good growth conditions in a greenhouse. In order to rule out any influence of the effects observed by any fungicidal action of the test compounds, it was additionally ensured that the tests proceeded without fungal infection and without infection pressure. After the recovery phase had ended, the intensities of damage were rated visually in comparison to untreated, unstressed controls of the same age (in the case of drought stress) or the same growth stage (in the case of cold stress). The intensity of damage was first recorded as a percentage (100 % = plants have died, 0 % = same as control plants). These values were then used to calculate the efficacy of the test compounds (percentage reduction in the intensity of damage as a result of substance application), and a final assessment of the respective efficacy was made, i.e. "0" = no effect, "+" = slight beneficial effect, "++" = significant beneficial effect, "+++" = strong beneficial effect against drought stress, "++++" = very strong effect superior to internal standard ABA.

**In vitro:** *ABI1-(AtRCAR11)*: The assay described hereinafter utilizes the inhibition of the phosphatase ABI1 via the co-regulator RCAR11/PYR1 from *Arabidopsis thaliana*. Expression and purification of RCARs and PP2Cs was performed as described.[4a,25] For the determination of activity, the dephosphorylation of 4-methylumbelliferyl phosphate (MUP) was measured at 460 nm. The in vitro assay was conducted in Greiner 384-well PS microplates F-well, using two controls: a) dimethyl sulfoxide (DMSO) 0.5 % (f.c.) and b) 5 µM (f.c.) abscisic acid (ABA). The assay described here was generally conducted with substance concentrations of the appropriate chemical test substances in a concentration range of 0.1 µM to 100 µM in a solution of DMSO and water. The substance solution thus obtained, if necessary, was stirred with esterase from porcine liver (EC 3.1.1.1) at room temperature for 3 h and centrifuged at 4000 rpm for 30 min. A total volume of 45 µL was introduced into each cavity of the microplate, having the following composition:

(1) 5 µL of substance solution, i.e. a) DMSO 5 % or b) abscisic acid solution or c) the corresponding example compound of the general formula (I) dissolved in 5 % DMSO.

(2) 20 µL of enzyme buffer mix, composed of a) 40 % by vol. of enzyme buffer [10 mL contain equal proportions by volume of 500 mM Tris-HCl pH8, 500 mM NaCl, 3.33 mM $MnCl_2$, 40 mM dithiothreitol (DTT)], b) 4 % by vol. of ABI1 dilution (protein stock solution was diluted so as to give, after addition, a final concentration in the assay of 0.15 µg ABI1/well), c) 4 % by vol. of RCAR11 dilution (enzyme stock was diluted so as to give, on addition of the dilution to the enzyme buffer mix, a final concentration in the assay of 0.30 µg enzyme/well), d) 5 % by vol. of Tween20 (1 %), e) 47 % by vol. $H_2O$ bi-distilled.

(3) 20 µL of substrate mix, composed of a) 10 % by vol. of 500 mM Tris-HCl pH8, b) 10 % by vol. of 500 mM NaCl, c) 10 % by vol. of 3.33 mM $MnCl_2$, d) 5 % by vol. of 25 mM MUP, 5 % by vol. of Tween20 (1 %), 60 % by vol. of $H_2O$ bi-distilled. Enzyme buffer mix and substrate mix were made up 5 min prior to the addition and warmed to a temperature of 35 °C. On completion of pipetting of all the solutions and on completion of mixing, the plate was incubated at 35 °C for 20 min. Finally, a relative fluorescence measurement was made at 35 °C with a BMG Labtech "POLARstar Optima" microplate reader using a 340/10 nm excitation filter and a 460 nm emission filter.

**X-ray Crystallography:** For structural studies RCAR11 and an N-terminally truncated version of HAB1 lacking residues 1–178 (ΔNHAB1) were expressed and purified according to published protocols.[26] Prior to crystallization RCAR11, ΔNHAB1 and ABA-analogue **11** or **16a** were mixed in 20 mM Tris pH 7.5, 150 mM NaCl, 1 mM $MnCl_2$, and 1 mM β-mercaptoethanol to final concentrations of 3 mg/mL, 5 mg/mL and 1 mM, respectively. Crystals were obtained by sitting drop vapor diffusion from 20 % Peg 8000, 100 mM Tris pH 8.5, 160 mM $MgCl_2$, 60 mM glycylglycylglycine at 18 °C. Diffraction data were collected on an Xcalibur Nova diffraction system from Oxford Diffraction. The structures were solved by molecular replacement with MOLREP[27] using the ternary complex of RCAR11, ΔNHAB1 and ABA (pdb accession code 3QN1) as a search model. The model was refined through successive rounds of manual model building using Coot[28] and restrained refinement using RefMac5.[29] Data processing and refinement statistics are shown in Table S1.

**Chemistry: General**: All reagent-grade solvents and chemicals were purchased from standard commercial suppliers and used without further purification. All non-aqueous reactions were carried out under anhydrous conditions using dry solvents. Reactions were monitored by LC-MS or TLC carried out on 0.25 mm silica gel plates (60F-254). TLC plates were visualized using UV light. Flash chromatography was carried out using Biotage Isolera One systems with pre-packed column cartridges (Biotage KP-Sil [40+M] or KP-Sil [25+M]), with typical gradients starting from a ethyl acetate/heptane ratio of 20:80 to a final ratio of 80:20. The $^1$H NMR, $^{13}$C NMR and $^{19}$F NMR spectroscopy data, which are reported for the chemical examples described below (400 MHz for $^1$H NMR and 150 MHz for $^{13}$C NMR and 375 MHz for $^{19}$F NMR, solvent: $CDCl_3$, $CD_3OD$ or [$D_6$]DMSO, internal standard: tetramethylsilane $\delta$ = 0.00 ppm), were obtained on a Bruker instrument, and the signals listed have the meanings given below: br = broad; s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of a doublet of doublets, m = multiplet, q = quartet, quint = quintet, sext = sextet, sept = septet, dq = doublet of quartets, dt = doublet of triplets. The abbreviations used for chemical groups are defined as follows: Me = $CH_3$, Et = $CH_2CH_3$, *t*Hex = $C(CH_3)_2CH(CH_3)_2$, *t*Bu = $C(CH_3)_3$, *n*Bu = unbranched butyl, *n*Pr = unbranched propyl, *c*Hex = cyclohexyl. In the case of diastereomeric mixtures, either the significant signals for each of the diastereomers or the characteristic signal of the main diastereomer are reported. Further experimental details are disclosed in the supplementary material, as well as in references.[22,23]

**1-(3-Hydroxy-4-methylpent-1-yn-3-yl)cyclopropanecarbonitrile (13a):** Triethylamine (510 mL, 3.71 mol) and pivaloyl chloride (106 mL, 1.02 mol) were added to a cooled solution (0 °C) of methoxymethylamine hydrochloride (100 g, 0.93 mol) in dichloromethane (1 L). The resulting reaction mixture was stirred at room temp. for 6 h and was diluted with water on completion of the reaction. Dichloromethane was added, and the aqueous layer was extracted thoroughly. The combined organic layer was washed with brine solution, dried with anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting crude product was purified over silica gel column chromatography by eluting with 20 % EtOAc/petroleum ether, and a portion (31 mL, 424 mmol) of

the resulting product was dissolved in tetrahydrofuran (400 mL) thereafter. After cooling to –78 °C, a solution of LDA in tetrahydrofuran (2 M, 250 mL, 501 mmol) was added, and the resulting reaction mixture was stirred at room temp. for 4 h. Upon complete turnover, the reaction mixture was quenched with ammonium chloride solution and was extracted with ethyl acetate. The combined organic layer was washed with brine solution, dried with anhydrous sodium sulfate, and the organic solvent was reduced under reduced pressure. The remaining residue was purified via column chromatography (silica gel, 20 % EtOAc/petroleum ether as eluent) to afford 1-isobutyrylcyclopropanecarbonitrile (35.0 g, 66 % of theoretical). 1-Isobutyrylcyclopropanecarbonitrile (4.00 g, 29.16 mmol) was then dissolved in tetrahydrofuran (120 mL) in a round-bottom flask under argon, cooled to 0 °C, and added dropwise to a solution of a lithium acetylide-ethylenediamine complex in tetrahydrofuran (4.11 g, 37.91 mmol, content 85 %, 80 mL). On completion of addition, the reaction solution was stirred at room temperature for 4 h, then water was added and the mixture was concentrated under reduced pressure. The remaining residue was admixed with water and dichloromethane, and the aqueous phase was extracted repeatedly with dichloromethane. The combined organic phases were dried with magnesium sulfate, filtered and concentrated under reduced pressure. By column chromatography purification of the crude product obtained (ethyl acetate/heptane gradient), 1-(3-hydroxy-4-methylpent-1-yn-3-yl)cyclopropanecarbonitrile **13a** (2.59 g, 54 % of theoretical) was isolated as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 2.48 (s, 1 H), 2.41 (sept, 1 H), 2.19 (br. s, 1 H, OH), 1.34–1.28 (m, 3 H), 1.21 (m, 1 H), 1.12 (d, 3 H), 1.09 (d, 3 H) ppm. HRMS-ESI: calcd. for $C_{10}H_{14}NO^+$ [M + H]$^+$ 164.2164, found 164.2149.

**1-(1-Cyclopentyl-1-hydroxyprop-2-yn-1-yl)cyclopropanecarbonitrile (13c):** 1-(Cyclopentylcarbonyl)cyclopropanecarbonitrile (9.00 g, 55.14 mmol) was dissolved in abs. tetrahydrofuran (50 mL) in a round-bottom flask under argon and added dropwise to a solution, cooled to 0 °C, of a lithium acetylide-ethylenediamine complex (6.59 g, 71.68 mmol) in tetrahydrofuran (40 mL). On completion of addition, the reaction solution was stirred at room temperature for 2 h, then water was added and the mixture was concentrated under reduced pressure. The remaining residue was admixed with water and $CH_2Cl_2$, and the aqueous phase was extracted repeatedly with $CH_2Cl_2$. The combined organic phases were dried with $MgSO_4$, filtered and concentrated under reduced pressure. By column chromatography purification of the crude product obtained (ethyl acetate/heptane gradient), 1-(1-cyclopentyl-1-hydroxyprop-2-yn-1-yl)-cyclopropanecarbonitrile **13c** (2.55 g, 25 % of theoretical) was isolated as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 2.65 (m, 1 H), 2.47 (s, 1 H), 2.18 (br. s, 1 H, OH), 1.97–1.85 (m, 2 H), 1.73–1.59 (m, 4 H), 1.45–1.39 (m, 1 H), 1.37–1.33 (m, 2 H), 1.30–1.26 (m, 2 H), 1.22–1.19 (m, 1 H) ppm.

**1-[(1*E*)-3-Hydroxy-4-methyl-1-(tributylstannyl)pent-1-en-3-yl]-cyclopropanecarbonitrile (14a):** Tetrakis(triphenylphosphine)-palladium(0) (198 mg, 0.17 mmol) was initially charged under argon in a flame-dried round-bottom flask, and abs. tetrahydrofuran (20 mL) and 1-(3-hydroxy-4-methylpent-1-yn-3-yl)cyclopropanecarbonitrile **13a** (560 mg, 3.41 mmol) were added. Stirring at room temperature for 5 min was followed by the addition of tributyltin hydride (1.10 mL, 4.12 mmol). The resulting reaction mixture was stirred at room temperature for 1 h and then water was added. The aqueous phase was repeatedly extracted thoroughly with $CH_2Cl_2$, and the combined organic phases were then dried with magnesium sulfate, filtered and concentrated under reduced pressure. By final column chromatography purification of the resulting crude product (ethyl acetate/heptane gradient), it was possible to obtain 1-[(1*E*)-3-hydroxy-4-methyl-1-(tributylstannyl)pent-1-en-3-yl]cyclopropanecarbonitrile **14a** (0.38 mg, 24 % of theoretical) in the form of a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.18 (d, 1 H), 6.03 (d, 1 H), 2.32 (sept, 1 H), 1.53–1.45 (m, 6 H), 1.35–1.29 (m, 6 H), 1.28 (m, 1 H), 1.14 (m, 1 H), 1.03 (d, 3 H), 0.94–0.88 (m, 18 H), 0.72 (m, 2 H) ppm. HRMS-ESI: calcd. for $C_{22}H_{42}NOSn^+$ [M + H]$^+$ 455.2772, found 455,2784.

**1-[(2*E*)-1-Cyclopentyl-1-hydroxy-3-(tributylstannyl)prop-2-en-1-yl]cyclopropanecarbonitrile (14c):** Tetrakis(triphenylphosphine)palladium(0) (464 mg, 0.40 mmol) was initially charged under argon in a flame-dried round-bottom flask, and tetrahydrofuran (30 mL) and 1-(1-cyclopentyl-1-hydroxyprop-2-yn-1-yl)cyclopropanecarbonitrile **13c** (1900 mg, 10.04 mmol) were added. Stirring at room temperature for 5 min was followed by the addition of tributyltin hydride (3.24 mL, 12.05 mmol). The resulting reaction mixture was stirred at room temperature for 1 h and then water was added. The aqueous phase was repeatedly extracted thoroughly with dichloromethane, and the combined organic phases were then dried with magnesium sulfate, filtered and concentrated under reduced pressure. By final column chromatography purification of the resulting crude product (ethyl acetate/heptane gradient), it was possible to obtain 1-[(2*E*)-1-cyclopentyl-1-hydroxy-3-(tributyl-stannyl)prop-2-en-1-yl]cyclopropanecarbonitrile **14c** (1650 mg, 34 % of theoretical) in the form of a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.19 (d, 1 H), 6.13 (d, 1 H), 2.63–2.57 (m, 1 H), 1.88–1.80 (br. s, 1 H, OH), 1.73–1.58 (m, 4 H), 1.56–1.47 (m, 8 H), 1.37–1.27 (m, 8 H), 1.26 (m, 1 H), 1.13 (m, 1 H), 1.05–0.98 (m, 2 H), 0.94–0.86 (m, 15 H) ppm. HRMS-ESI: calcd. for $C_{24}H_{44}NOSn^+$ [M + H]$^+$ 481.3137, found 481.3131.

**(2*Z*,4*E*)-6-(1-Cyanocyclopropyl)-3-ethyl-6-hydroxy-7-methyl-octa-2,4-dienoic Acid (16c):** Pent-2-ynecarboxylic acid (1500 mg, 15.2 mmol) was dissolved in concenctrated acetic acid (15 mL), finely powdered sodium iodide (6876 mg, 45.8 mmol) was added and the mixture was stirred at a temperature of 110 °C for 3 h. After cooling to room temperature, methyl *tert*-butyl ether (MTBE) and saturated sodium thiosulfate solution were added. The aqueous phase was extracted repeatedly with MTBE, and the combined organic phases were dried with magnesium sulfate, filtered and concentrated under reduced pressure. By column chromatography purification of the resulting crude product (ethyl acetate/heptane gradient), it was possible to obtain (2*Z*)-3-iodopent-2-enoic acid (2100 mg, 58 % of theoretical) in the form of a colorless solid. 1-[(1*E*)-3-Hydroxy-4-methyl-1-(tributylstannyl)pent-1-en-3-yl]cyclopropane-carbonitrile **14a** (390 mg, 0.86 mmol) and (2*Z*)-3-iodopent-2-enoic acid (194 mg, 0.86 mmol) were dissolved in *N*,*N*-dimethylformamide (4 mL) under argon in a flame-dried round-bottom flask, dichloro[bis(acetonitrile)palladium(II)] (7 mg, 0.03 mmol) and copper(I) iodide (131 mg, 0.80 mmol) were added and the mixture was stirred at room temperature for 8 h. After the addition of aqueous potassium fluoride solution, stirring of the reaction mixture continued at room temperature for 1 h. The aqueous phase was then repeatedly extracted thoroughly with dichloromethane, and the combined organic phases were then dried with magnesium sulfate, filtered and concentrated under reduced pressure. By final column chromatography purification of the resulting crude product (ethyl acetate/heptane gradient), it was possible to obtain (2*Z*,4*E*)-6-(1-cyanocyclopropyl)-3-ethyl-6-hydroxy-7-methylocta-2,4-dienoic acid **16c** (83 mg, 37 % of theoretical) in the form of a colorless viscous oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.63 (d, 1 H), 6.28 (d, 1 H), 5.81 (s, 1 H), 2.97 (br. s, 1 H, OH), 2.89 (br. s, 1 H, OH), (s, 3 H), 2.43 (q, 2 H), 2.38 (sept, 1 H), 1.33 (m, 1 H) 1.21 (m, 1 H), 1.18 (t, 3 H), 1.09 (d, 3 H), 1.05 (m, 1 H), 0.97 (d, 3 H) ppm. $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 170.5; 162.8; 157.4; 138.2; 125.8; 122.8; 115.9; 74.8; 36.6; 31.5;

27.6; 17.4; 16.5; 12.5; 10.3 ppm. LC-MS (ret.-time, min, [$M^+$/log *p*]) 1.04 [263.33/2.15]. HRMS-ESI: calcd. for $C_{15}H_{23}NO_3^+$ [M + H]$^+$ 264.1521, found 264,1558.

**(*S*)- and (*R*)-(2*Z*,4*E*)-6-(1-Cyanocyclopropyl)-3-ethyl-6-hydroxy-7-methylocta-2,4-dienoic Acid [(*S*)-16c, (*R*)-16c]:** Enantiomers of (2*Z*,4*E*)-6-(1-cyanocyclopropyl)-3-ethyl-6-hydroxy-7-methylocta-2,4-dienoic acid **16c** were also separated carefully via chiral prep. HPLC to afford **(*S*)-16c**, retention time 19.607, $[\alpha]_D^{20}$ = –280 and **(*R*)-16c**, ret. time 23.692, $[\alpha]_D^{20}$ = +289 (chiral HPLC analysis: Chiralpak IG 250/4.6 mm, flow rate 0.6 mL/min, eluent *n*-heptan/2-propanol 90:10).

**Methyl (2*E*,4*E*)-6-(1-Cyanocyclopropyl)-6-hydroxy-7-methyl-3-(tri-fluoromethyl)octa-2,4-dienoate (16e):** Methyl 4,4,4-trifluoro-but-2-ynoate (500 mg, 3.01 mmol) was dissolved in concentrated acetic acid (6 mL), finely powdered sodium iodide (1353 mg, 9.03 mmol) was added and the mixture was stirred at a temperature of 110 °C for 4 h. After cooling to room temperature, methyl *tert*-butyl ether (MTBE) and saturated sodium thiosulfate solution were added. The aqueous phase was extracted repeatedly with MTBE, and the combined organic phases were dried with magnesium sulfate, filtered and concentrated under reduced pressure. By column chromatography purification of the resulting crude product (ethyl acetate/heptane gradient), it was possible to obtain methyl (2*Z*)-4,4,4-trifluoro-3-iodobut-2-enoate (380 mg, 43 % of theoretical) in the form of a viscous oil. 1-[(1*E*)-3-hydroxy-4-methyl-1-(tributylstannyl)pent-1-en-3-yl]cyclopropanecarbonitrile **14a** (300 mg, 0.66 mmol) and methyl (2*Z*)-4,4,4-trifluoro-3-iodobut-2-enoate (185 mg, 0.66 mmol) were dissolved in *N*,*N*-dimethylformamide (20 mL) under argon in a flame-dried round-bottom flask, tetrakis(triphenylphosphine)palladium(0) (76 mg, 0.07 mmol) and copper(I) iodide (94 mg, 0.49 mmol) were added and the mixture was stirred at room temperature for 16 h. After the addition of aqueous potassium fluoride solution, stirring of the reaction mixture continued at room temperature for 1 h. The aqueous phase was then repeatedly extracted thoroughly with dichloromethane, and the combined organic phases were then dried with magnesium sulfate, filtered and concentrated under reduced pressure. By final column chromatography purification of the resulting crude product (ethyl acetate/heptane gradient), it was possible to obtain methyl (2*E*,4*E*)-6-(1-cyanocyclopropyl)-6-hydroxy-7-methyl-3-(trifluoromethyl)octa-2,4-dienoate **16e** (53 mg, 25 % of theoretical) in the form of a colorless viscous oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.44 (d, 1 H), 6.36 (d, 1 H), 6.32 (s, 1 H), 3.80 (s, 3 H), 2.42 (sept, 1 H), 1.63 (br. s, 1 H, OH), 1.27 (m, 1 H) 1.22 (m, 1 H), 1.12 (m, 1 H), 1.05 (d, 3 H), 0.99 (m, 1 H), 0.97 (d, 3 H) ppm. HRMS-ESI: calcd. for $C_{15}H_{19}NO_3F_3^+$ [M + H]$^+$ 318.3043, found 318,3027.

**Ethyl (2*E*,4*E*)-6-(1-Cyanocyclopropyl)-6-cyclopentyl-6-hydroxy-3-(trifluoromethyl)hexa-2,4-dienoate (16t):** Ethyl 4,4,4-trifluoro-but-2-ynoate (500 mg, 3.01 mmol) was dissolved in concentrated acetic acid (6 mL), finely powdered sodium iodide (1353 mg, 9.03 mmol) was added and the mixture was stirred at a temperature of 110 °C for 4 h. After cooling to r.t., methyl *tert*-butyl ether (MTBE) and saturated sodium thiosulfate solution were added. The aqueous phase was extracted repeatedly with MTBE, and the combined organic phases were dried with $MgSO_4$, filtered and concentrated. under reduced pressure. By column chromatography purification of the resulting crude product (ethyl acetate/heptane gradient), it was possible to obtain ethyl (2*Z*)-4,4,4-trifluoro-3-iodobut-2-enoate (380 mg, 45 % of theoretical) in the form of a viscous oil. 1-[(2*E*)-1-Cyclopentyl-1-hydroxy-3-(tributylstannyl)prop-2-en-1-yl]cyclopropanecarbonitrile **14c** (350 mg, 0.73 mmol) and ethyl (2*Z*)-4,4,4-trifluoro-3-iodobut-2-enoate (214 mg, 0.73 mmol) were dissolved in *N*,*N*-dimethylformamide (4 mL) under argon in a flame-dried round-bottom flask, dichlorobis(acetonitrile)-palladium(II) (6 mg, 0.02 mmol) and copper(I) iodide (111 mg, 0.58 mmol) were added and the mixture was stirred at room temperature for 12 h. After the addition of aqueous potassium fluoride solution, stirring of the reaction mixture continued at r.t. for 1 h. The aqueous phase was then repeatedly extracted thoroughly with $CH_2Cl_2$, and the combined organic phases were then dried with $MgSO_4$, filtered and concentrated under reduced pressure. By final column chromatography purification of the resulting crude product (ethyl acetate/heptane gradient), it was possible to obtain ethyl (2*E*,4*E*)-6-(1-cyanocyclopropyl)-6-cyclopentyl-6-hydroxy-3-(trifluoromethyl)hexa-2,4-dienoate **16t** (84 mg, 32 % of theoretical) in the form of a colorless viscous oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.49 (d, 1 H), 6.41 (d, 1 H), 6.31 (s, 1 H), 4.26 (q, 2 H), 2.69–2.63 (m, 1 H), 1.95–1.88 (m, 1 H), 1.68–1.60 (m, 4 H), 1.58 (br. s, 1 H, OH), 1.48–1.26 (m, 6 H) 1.19 (m, 1 H), 1.12 (m, 1 H), 1.03 (m, 1 H) ppm. HRMS-ESI: calcd. for $C_{18}H_{23}NO_3F_3^+$ [M + H]$^+$ 358.3672, found 358.3679.

**Methyl (2*Z*)-6-(1-Cyanocyclopropyl)-3-ethyl-6-hydroxy-7-methyloct-2-en-4-ynoate (17d):** Methyl pent-2-ynoate (14.48 mmol) was dissolved in concentrated acetic acid (15 mL), powdered sodium iodide (43.43 mmol) was added and the mixture was stirred at a temperature of 110 °C for 3 h. After cooling to room temp., methyl *tert*-butyl ether (MTBE) and saturated sodium thiosulfate solution were added. The aqueous phase was extracted repeatedly with MTBE, and the combined organic phases were dried with magnesium sulfate, filtered and concentrated under reduced pressure. By column chromatography purification of the resulting crude product (ethyl acetate/heptane gradient), it was possible to obtain methyl (2*Z*)-3-iodopent-2-enoate (about 3.0 g, 72 % of theoretical) in the form of a viscous oil. Copper(I) iodide (5 mg, 0.25 mmol) and bis(triphenylphosphine)palladium(II) chloride (13 mg, 0.02 mmol) were initially charged under argon in a flame-dried round-bottom flask, and toluene (2 mL) and methyl (2*Z*)-3-iodopent-2-enoate (151 mg, 0.63 mmol) were added. Stirring at room temp. for 10 min was followed by addition of a solution of 1-(3-hydroxy-4-methyl-pent-1-yn-3-yl)cyclopropanecarbonitrile **13a** (100 mg, 0.63 mmol) (120 mg, 0.63 mmol) in toluene (3 mL) and of diisopropylamine (0.26 mL, 1.88 mmol). The resulting reaction mixture was stirred at room temp. for 3 h and then water was added. The aqueous phase was extracted repeatedly with dichloromethane. The combined organic phases were dried with magnesium sulfate, filtered and concentrated under reduced pressure. By final column chromatography purification of the crude product obtained (using an ethyl acetate/heptane gradient), methyl (2*Z*)-6-(1-cyanocyclopropyl)-3-ethyl-6-hydroxy-7-methyloct-2-en-4-ynoate **17d** (149 mg, 78 % of theoretical) was isolated in the form of a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.02 (s, 1 H), 3.72 (s, 3 H), 2.63 (br. s, 1 H, OH), 2.28 (q, 2 H), 1.99 (m, 1 H), 1.88 (m, 1 H), 1.78 (m, 1 H), 1.50–1.41 (m, 4 H), 1.34 (m, 1 H), 1.24 (m, 1 H), 1.15 (t, 3 H), 1.06 (t, 6 H) ppm. $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 165.3; 139.6; 124.1; 121.6; 96.4; 85.4; 63.4; 51.4; 37.8; 31.9; 18.3; 17.5; 13.9; 12.7; 11.1 ppm. LC-MS (ret. time, min, [$M^+$/log *p*]) 2.84 [275.15/1.37]. HRMS-ESI: calcd. for $C_{16}H_{22}NO_3^+$ [M + H]$^+$ 276.3431, found 276,3408.

**Ethyl (2*Z*)-6-(1-Cyanocyclopropyl)-3-cyclopropyl-6-hydroxy-7-methyloct-2-en-4-ynoate (17i):** Ethyl 3-cyclopropylprop-2-ynoate (2.00 g, 14.48 mmol) was dissolved in concentrated acetic acid (15 mL), finely powdered sodium iodide (6.51 g, 43.43 mmol) was added and the mixture was stirred at a temperature of 110 °C for 3 h. After cooling to room temperature, methyl *tert*-butyl ether (MTBE) and saturated sodium thiosulfate solution were added. The aqueous phase was extracted repeatedly with MTBE, and the combined organic phases were dried with magnesium sulfate, filtered

and concentrated under reduced pressure. By column chromatography purification of the resulting crude product (ethyl acetate/heptane gradient), it was possible to obtain ethyl (2*Z*)-3-cyclopropyl-3-iodoacrylate (3.01 g, 74 % of theoretical) in the form of a viscous oil. Copper(I) iodide (47 mg, 0.25 mmol) and bis(triphenylphosphine)palladium(II) chloride (129 mg, 0.18 mmol) were initially charged under argon in a flame-dried round-bottom flask, and toluene (6 mL) and ethyl (2*Z*)-3-cyclopropyl-3-iodoacrylate (326 mg, 1.23 mmol) were added. Stirring at room temperature for 10 min was followed by the dropwise addition of a solution of 1-(3-hydroxy-4-methylpent-1-yn-3-yl)cyclopropanecarbonitrile **13a** (200 mg, 1.23 mmol) in toluene (9 mL) and of diisopropylamine (0.34 mL, 2.45 mmol). The resulting reaction mixture was stirred at room temp. for 3 h and then water was added. The aqueous phase was extracted repeatedly with $CH_2Cl_2$. The combined organic phases were dried with $MgSO_4$, filtered and concentrated under reduced pressure. By final column chromatography purification of the crude product obtained (using an ethyl acetate/heptane gradient), ethyl (2*Z*)-6-(1-cyanocyclopropyl)-3-cyclopropyl-6-hydroxy-7-methyloct-2-en-4-ynoate **17i** (190 mg, 47 % of theoretical) was isolated in the form of a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.17 (s, 1 H), 4.17 (q, 2 H), 2.46 (sept, 1 H), 2.01 (br. s, 1 H, OH), 1.68 (m, 1 H), 1.47 (m, 1 H), 1.39 (m, 1 H), 1.30 (m, 1 H), 1.28 (t, 3 H), 1.21 (m, 1 H), 1.12 (d, 3 H), 1.09 (d, 3 H), 0.87 (m, 4 H) ppm. HRMS-ESI: calcd. for $C_{18}H_{24}NO_3^+$ [M + H]$^+$ 302.3803, found 302.3798.

**1-(3-Hydroxy-4-methylpent-1-yn-3-yl)cyclobutanecarbonitrile (19a):** 1-Isobutyrylcyclobutanecarbonitrile (9.00 g, 60.0 mmol) was dissolved in tetrahydrofuran (50 mL) in a round-bottom flask under argon and added dropwise to a solution, cooled to 0 °C, of a lithium acetylide-ethylenediamine complex (7.92 g, 77.0 mmol, content 90 %) in tetrahydrofuran (20 mL). On completion of addition, the reaction solution was stirred at room temp. for 2 h, then water was added and the mixture was concentrated under reduced pressure. The remaining residue was admixed with water and dichloromethane, and the aqueous phase was extracted repeatedly with dichloromethane. The combined organic phases were dried with $MgSO_4$, filtered and concentrated under reduced pressure. By chromatography purification of the crude product obtained (ethyl acetate/heptane gradient), 1-(3-hydroxy-4-methylpent-1-yn-3-yl)cyclobutanecarbonitrile **19a** (2.50 g, 24 % of theoretical) was isolated as a colorless waxy solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 2.70 (m, 2 H), 2.64 (s, 1 H), 2.36 (m, 2 H), 2.24 (m, 2 H), 2.12 (br. s, 1 H, OH), 1.08 (d, 3 H), 0.98 (d, 3 H) ppm. HRMS-ESI: calcd. for $C_{11}H_{16}NO^+$ [M + H]$^+$ 178.2430, found 178.2404.

**1-[(1*E*)-3-Hydroxy-4-methyl-1-(tributylstannyl)pent-1-en-3-yl]-cyclobutanecarbonitrile (20a):** Tetrakis(triphenylphosphine)palladium(0) (261 mg, 0.23 mmol) was initially charged under argon in a flame-dried round-bottom flask, and tetrahydrofuran (20 mL) and 1-(3-hydroxy-4-methylpent-1-yn-3-yl)cyclobutanecarbonitrile (1000 mg, 5.64 mmol) were added. Stirring at room temp. for 5 min was followed by the addition of tributyltin hydride (1.82 mL, 6.77 mmol). The resulting reaction mixture was stirred at room temp. for 1 h and then water was added. The aqueous phase was repeatedly extracted with dichloromethane, and the combined organic phases were then dried with magnesium sulfate, filtered and concentrated under reduced pressure. By final column chromatography purification of the resulting crude product (ethyl acetate/heptane gradient), it was possible to obtain 1-[(1*E*)-3-hydroxy-4-methyl-1-(tributylstannyl)-pent-1-en-3-yl]cyclobutane-carbonitrile **20a** (1.40 g, 53 % of theoretical) in the form of a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.23 (d, 1 H), 5.98 (d, 1 H), 2.78 (m, 1 H), 2.30 (m, 1 H), 2.22 (m, 3 H), 2.02 (m, 1 H), 1.77 (m, 1 H), 1.67 (br. s, 1 H, OH), 1.53–1.45 (m, 6 H), 1.35–1.27 (m, 6 H), 0.96–0.85 (m, 21 H) ppm. HRMS-ESI: calcd. for $C_{23}H_{43}NOSn^+$ [M + H]$^+$ 468.3038, found 468.3029.

**Methyl (2*E*,4*E*)-6-(1-Cyanocyclobutyl)-6-hydroxy-7-methyl-3-(trifluoromethyl)octa-2,4-dienoate (21e):** Methyl 4,4,4-trifluorobut-2-ynoate (500 mg, 3.01 mmol) was dissolved in concentrated acetic acid (6 mL), finely powdered sodium iodide (1353 mg, 9.03 mmol) was added and the mixture was stirred at a temperature of 110 °C for 4 h. After cooling to room temp., MTBE and saturated sodium thiosulfate solution were added. The aqueous phase was extracted repeatedly with MTBE, and the combined organic phases were dried with magnesium sulfate, filtered and concentrated under reduced pressure. By column chromatography purification of the resulting crude product (ethyl acetate/heptane gradient), it was possible to obtain methyl (2*Z*)-4,4,4-trifluoro-3-iodobut-2-enoate (380 mg, 43 % of theoretical) in the form of a viscous oil. 1-[(1*E*)-3-Hydroxy-4-methyl-1-(tributylstannyl)pent-1-en-3-yl]cyclobutane-carbonitrile **20a** (300 mg, 0.64 mmol) and methyl (2*Z*)-4,4,4-trifluoro-3-iodobut-2-enoate (179 mg, 0.64 mmol) were dissolved in *N*,*N*-dimethylformamide (5 mL) under argon in a flame-dried round-bottom flask, dichlorobis(acetonitrile)palladium(II) (5 mg, 0.02 mmol) and copper(I) iodide (98 mg, 0.51 mmol) were added and the mixture was stirred at room temp. for 12 h. After adding KF solution, stirring of the reaction mixture continued at room temperature for 1 h. The aqueous phase was then repeatedly extracted with diethyl ether, and the combined organic phases were then dried with magnesium sulfate, filtered and concentrated under reduced pressure. By final column chromatography purification of the resulting crude product (ethyl acetate/heptane gradient), it was possible to obtain methyl (2*E*,4*E*)-6-(1-cyanocyclobutyl)-6-hydroxy-7-methyl-3-(trifluoromethyl)octa-2,4-dienoate **21e** (46 mg, 21 % of theoretical) in the form of a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.53 (d, 1 H), 6.31 (s, 1 H), 6.30 (d, 1 H), 3.80 (s, 3 H), 2.65 (m, 1 H), 2.40 (m, 1 H), 2.29 (m, 2 H), 2.11 (m, 1 H), 1.80 (m, 1 H), 1.73 (br. s, 1 H, OH), 1.30 (m, 1 H), 0.94 (d, 3 H), 0.91 (d, 3 H) ppm. HRMS-ESI: calcd. for $C_{16}H_{20}NO_3F_3^+$ [M + H]$^+$ 331.3303, found 331.3295.

**Methyl (2*Z*)-6-(1-Cyanocyclobutyl)-6-hydroxy-7-methyl-3-trifluoro-methyloct-2-en-4-ynoate (22e):** Methyl 4,4,4-trifluorobut-2-ynoate (500 mg, 3.01 mmol) was dissolved in concentrated acetic acid (6 mL), finely powdered sodium iodide (1353 mg, 9.03 mmol) was added and the mixture was stirred at a temperature of 110 °C for 4 h. After cooling to room temperature, MTBE and saturated sodium thiosulfate solution were added. The aqueous phase was extracted repeatedly with MTBE, and the combined organic phases were dried with magnesium sulfate, filtered and concentrated under reduced pressure. By column chromatography purification of the resulting crude product (ethyl acetate/heptane gradient), it was possible to obtain methyl (2*Z*)-4,4,4-trifluoro-3-iodobut-2-enoate (380 mg, 43 % of theoretical) in the form of a viscous oil. Copper(I) iodide (6 mg, 0.03 mmol) and bis(triphenylphosphine)palladium(II) chloride (18 mg, 0.03 mmol) were initially charged under argon in a flame-dried round-bottom flask, and toluene (6 mL) and methyl (2*Z*)-4,4,4-trifluoro-3-iodobut-2-enoate (237 mg, 0.85 mmol) were added. Stirring at room temperature for 10 min was followed by the dropwise addition of a solution of 1-(3-hydroxy-4-methylpent-1-yn-3-yl)cyclobutanecarbonitrile **19a** (150 mg, 0.85 mmol) in toluene (7 mL) and of diisopropylamine (0.36 mL, 2.54 mmol). The resulting reaction mixture was stirred at room temp. for 3 h and then water was added. The aqueous phase was extracted repeatedly with dichloromethane. The combined organic phases were dried with $MgSO_4$, filtered and concentrated under reduced pressure. By final column chromatography of the crude product obtained (using an ethyl acetate/heptane gradient), methyl (2*Z*)-6-(1-cyanocyclobutyl)-6-hydroxy-7-methyl-3-trifluoromethyloct-2-en-4-ynoate **22e**

(147 mg, 53 % of theoretical) was isolated in the form of a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.71 (s, 1 H), 3.83 (s, 3 H), 2.79–2.68 (m, 2 H), 2.47 (br. s, 1 H, OH), 2.41 (m, 4 H), 2.32 (m, 2 H), 1.94 (m, 1 H), 1.13 (d, 3 H), 1.03 (d, 3 H) ppm. HRMS-ESI: calcd. for $C_{16}H_{19}NO_3F_3^+$ $[M + H]^+$ 330.1215, found 330.1209.

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