Total Synthesis

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Polyunsaturated C-Glycosidic 4-Hydroxy-2-pyrone Derivatives: Total Synthesis Shows that Putative Orevactaene Is Likely Identical with Epipyrone A

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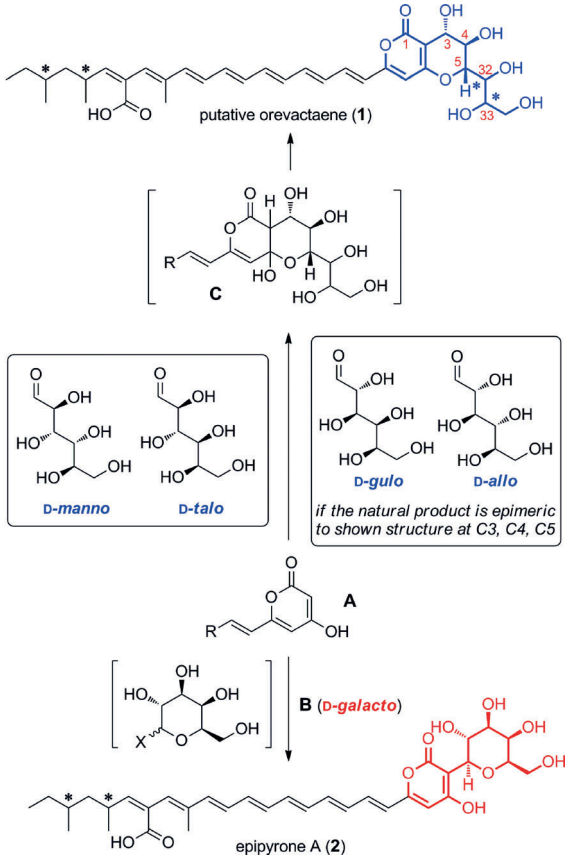
Dedicated to Prof. Herbert Waldmann on the occasion of his 60th birthday

Abstract: *Orevactaene and epipyrone A were previously thought to comprise the same polyunsaturated tail but notably different C-glycosylated 4-hydroxy-2-pyrone head groups. Total synthesis now shows that the signature bicyclic framework assigned to orevactaene is a chimera; the compound is almost certainly identical with epipyrone A, whose previously unknown stereochemistry has also been established during this study. Key to success was the ready formation of the bicyclic core of putative orevactaene by a sequence of two alkyne cycloisomerization reactions using tungsten and gold catalysis. Equally important was the flexibility in the assembly process gained by the use of heterobimetallic polyunsaturated modules whose termini could be selectively and consecutively addressed in a practical one-pot cross-coupling sequence.*

Orevactaene (**1**, also called BMS-213438)[1] and epipyrone A (**2**, also called D8646-2-6)[2,3] are the most noteworthy representatives of an exceedingly rare chemotype comprising a 4-hydroxy-2-pyrone nucleus decorated with a C-glycosidic substituent and a polyunsaturated side chain (Scheme 1).[4] Both compounds were isolated from *Epicoccum purpurascens* (syn. *E. nigrum*) strains; whereas **1** exhibits HIV-1 inhibitory properties,[1] **2** and congeners were originally described as telomerase inhibitors;[2] later on, **2** was found to show significant activity against the influenza A virus (H1N1) and was also patented for use as a fungicide.[3,5] While these intriguing natural products seem to share an identical conjugated heptaene tail terminated by a dimethyl-branched pentyl chain of as yet unknown configuration, they ostensibly differ in their signature head groups: **2** features a regular β-C-glycosidic link between a 4-hydroxy-2-pyrone and a galactopyranosyl ring, whereas the pyrone and the carbohydrate part in **1** are thought to be annulated.[6] No information as to the configuration of the two chiral centers C32 and C33 *exo* to the bicyclic core is available; for the annulated ring itself, the large ^3J coupling constants (9.3–9.5 Hz) between H3, H4, and H5 seem to indicate an all-*trans* orientation of the substituents.[1] This particular relative stereochemistry, however, implies that the incorporated sugar cannot be galactose as present in **2** but must either be mannose, talose, gulose, or allose. In addition, the absolute configurations of **1** and **2** are also unknown (Scheme 1).



Scheme 1. Structures and presumed biosynthesis of putative orevactaene (**1**) and epipyrone A (**2**); the stereochemistry at the chiral centers marked * as well as the absolute configuration of either natural product are unknown.

Ironically, it turns out that the isolation team was profoundly misled by what appeared to be a seemingly secure piece of stereochemical information. As will become evident below, it is the spectroscopic fingerprint of uniformly large ^3J couplings between H3, H4, and H5 that confirmed that orevactaene cannot contain an annulated backbone as originally proposed.[1] Rather, all evidence suggests that orevactaene is identical with epipyrone A.

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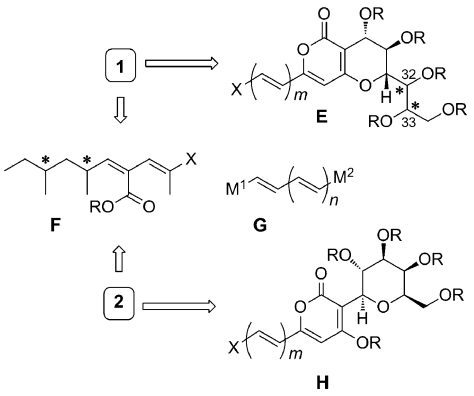


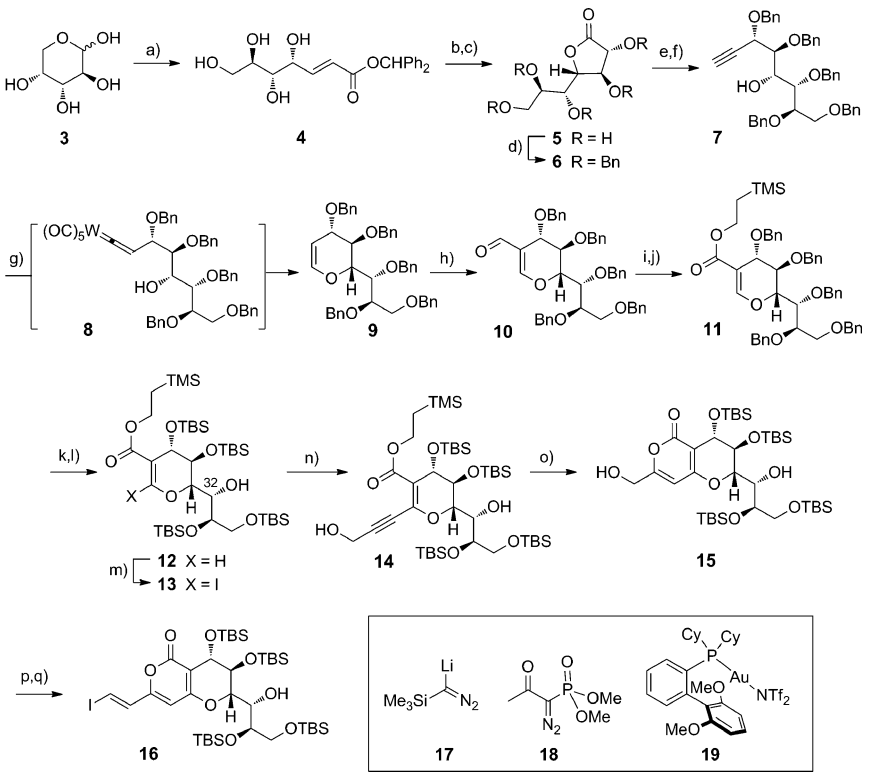
Scheme 2. Retrosynthetic analysis. M = metal or metalloid, R = generic protecting group, X = halide.

The few studies previously directed towards these intricate targets had left the questions concerning constitution and stereostructure open.[7,8] In view of five-plus-two basically unassigned chiral centers located in two separated clusters at the head and the tail region of **1**, respectively, one has to be prepared to make a library of isomers to clarify this point. Only a highly convergent approach that assembles building blocks of unambiguous stereostructure may succeed. We opted for a "stitching" assembly mode, in which a heterodimetalated linchpin **G** allows any combination of the head and tail pieces **E** and **F** to be connected in a single operation (Scheme 2).[9] This strategy, however, must also take the sensitivity of the polyunsaturated fragments and products into consideration. It appeared to us that a dissymmetric tetraene-diyl derivative **G** ($M^1 \neq M^2$, $n = 3$) might be the best compromise in terms of accessibility, reactivity, and stability. Conceptually, epipyrone A (**2**) can be disconnected in a similar manner into building blocks of type **F**, **G**, and **H**.

Alkyl chains featuring 1,3-*syn*- or 1,3-*anti*-configured methyl branches are known to populate sufficiently different conformational space as to render their spectral signatures dissimilar.[10] One can therefore expect that the configuration of the two as yet unassigned chiral centers in the tail region of **1** can be firmly established by spectroscopic means. We were not sure, however, that the same level of confidence could be reached for the two hydroxylated centers at C32 and C33 in the polar tail branching off the head piece. Therefore, we deliberately chose carbohydrates as starting materials to define these two critical sites in fragment **E**. The price to pay for the stereochemical rigor might be the effort that it takes to prepare the necessary isomeric building blocks by separate routes. As will become evident below, however, this proved unnecessary in the end.

Our first foray commenced with D-arabinose (**3**; Scheme 3). Chain extension by Wittig olefination gave (*E*)-**4**, which was detained from undergoing spontaneous oxa-Michael reactions by the crowded diphenylmethyl ester group.[11,12] The subsequent dihydroxylation followed Kishi's rule[13] and led to the *manno*-configured γ-lactone **5** after acid treatment of the crude material. Perbenzylation of the hydroxy groups was carried out under acidic conditions to avoid epimerization adjacent to the lactone. DIBAL-H reduction of **6** then set the stage for a one-carbon homologation to the corresponding terminal alkyne **7**, which proceeded well upon addition of lithiated TMS-diazomethane (**17**),[14] whereas attempted use of the Bestmann–Ohira reagent **18** was to no avail.

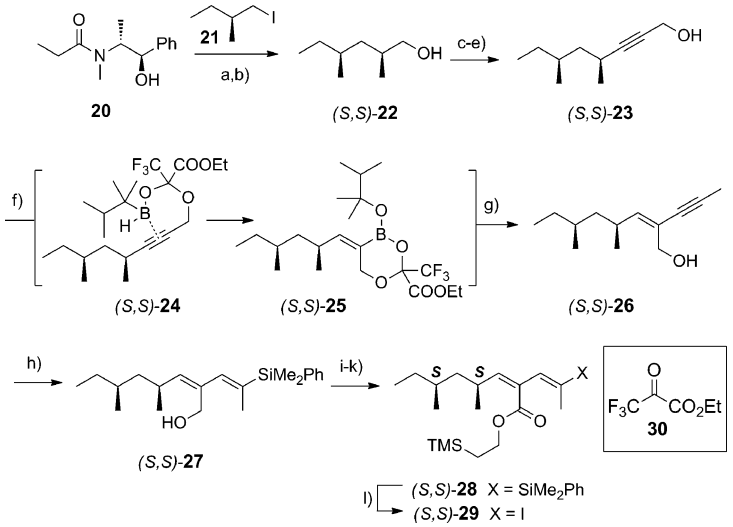
Next, compound **7** was transformed into glycal **9** by treatment with catalytic amounts of $[W(CO)_6]$ and DABCO under UV irradiation.[15] Upon loss of a CO group, the coordinatively unsaturated catalyst converts the terminal alkyne into the corresponding alkenylidene complex **8**, which is intercepted by the tethered -OH group. Although the same



Scheme 3. a) $Ph_3P{=}CHCOOCHPh_2$, 1,4-dioxane, DMF, 61%; b) OsO_4 cat., NMO·H_2O, acetone/H_2O; c) Amberlyst IR-120H$^+$, Et_2O, H_2O, 72% (over 2 steps); d) $BnOC(NH)CCl_3$, TfOH, 1,4-dioxane, 74%; e) DIBAL-H, CH_2Cl_2, 85%; f) LDA, $TMSCHN_2$, THF, 65%; g) $[W(CO)_6]$ (15 mol%), DABCO, THF, *hν*, 68%; h) $POCl_3$, DMF, 65%; i) $NaClO_2$, NaH_2PO_4, H_2O_2, MeCN, *t*BuOH, H_2O, 77%; j) 2-(trimethylsilyl)ethanol, Ph_3P, DEAD, THF, 80%; k) H_2, $Pd(OH)_2$/C cat., MeOH; l) TBSOTf, pyridine, CH_2Cl_2, 95% (over 2 steps); m) LDA, I_2, THF, 71%; n) propargyl alcohol, $[(Ph_3P)_2PdCl_2]$ (10 mol%), CuI (20 mol%), NEt_3, 85%; o) **19** (1 mol%), $MeNO_2$, 82%; p) DMP, CH_2Cl_2, 90%; q) CHI_3, $CrCl_2$, THF, 57%. Bn = benzyl, DABCO = 1,4-diazabicyclo-[2.2.2]octane, DEAD = diethyl azodicarboxylate, DMP = Dess–Martin periodinane, LDA = lithium diisopropylamide, NMO = *N*-methylmorpholine *N*-oxide, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl, Ts = *para*-toluenesulfonyl.

net 6-*endo*-dig cyclization can also be achieved with catalytic [(Ph_3P)RhCl] in DMF,[16] the tungsten-based procedure proved to be better scalable.

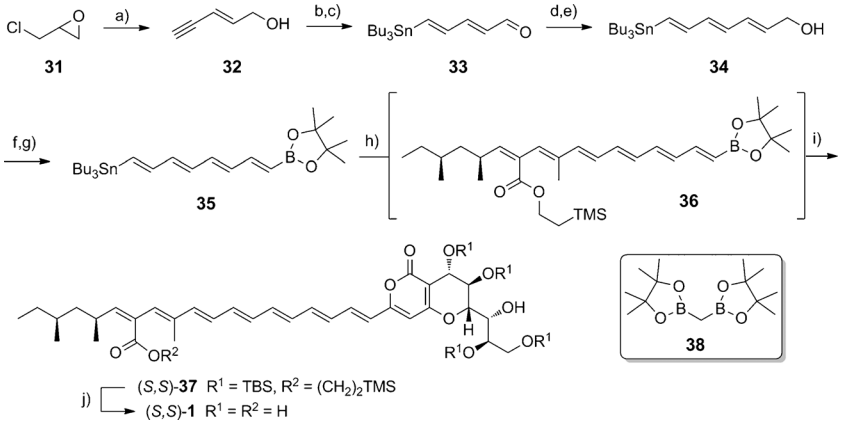
By virtue of the polarization of the enol ether, the subsequent Vilsmeier–Haack formylation of **9** gave aldehyde **10** exclusively,[17] which was transformed into the corresponding ester **11**. While robust benzyl ethers had been necessary as protecting groups up to this point, it seemed prudent to replace them by TBS ethers to avoid any hassle during the final deprotection of the polyunsaturated target compound. To this end, **11** was subjected to hydrogenolysis, which left the push–pull alkene site intact; the resulting product was treated with TBSOTf/pyridine to give **12** in excellent yield, leaving the C32 hydroxy group (orevactaene numbering) uncapped for steric reasons. The use of an extra equivalent of LDA sufficed to prevent this protic site from intervening in the subsequent directed lithiation/iodination of the enol, whereas the hydroxy group is uncritical anyway in the Sonogashira coupling of the resulting iodide **13** with propargyl alcohol. Compound **14** was then cyclized with the help of gold complex **19** as a π-acidic catalyst[18] to the desired 2-pyrone **15** according to a procedure previously developed by our group.[19,20] This gratifying result adds another entry to the growing list of exigent pyrone derivatives prepared by this method.[19–21] Selective oxidation of the primary hydroxy group in **15** followed by a Takai olefination[22] furnished product **16** as a first fully functional building block en route to **1**.



Scheme 4. a) **21**, LDA, LiCl, THF, 79%; b) LDA, $BH_3{\cdot}NH_3$, THF, 75%; c) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; d) CBr_4, PPh_3, CH_2Cl_2; e) *n*BuLi, THF, then $(CH_2O)_n$, 51% (over 3 steps); f) i) **30**, THF, then thexylborane; ii) trimethylamine *N*-oxide; g) 1-iodopropyne, [(dppf)$PdCl_2$] (10 mol%), aq. KOH, 57%; h) $PhMe_2SiLi$, CuCN, THF, 90%; i) DMP, CH_2Cl_2, 92%; j) $NaClO_2$, $NaHPO_4$, H_2O_2, *t*BuOH, H_2O; k) 2-(trimethylsilyl)ethanol, DEAD, PPh_3, 62% (over 2 steps); l) NIS, 2,6-lutidine, hexafluoroisopropanol, 89%. dppf = 1,1′-bis(diphenylphosphino)ferrocene, NIS = *N*-iodosuccinimide.

For its reliability, auxiliary-controlled enolate alkylation was used for the preparation of all possible isomers of the tail region;[23] this route is explicitly spelled out for the *S*,*S* series in Scheme 4. Alcohol **22** was oxidized and the resulting aldehyde transformed into propargyl alcohol **23** by a Corey–Fuchs reaction, in which the lithiated alkyne primarily formed was quenched with paraformaldehyde.[24] This compound was then subjected to directed hydroboration/cross-coupling as concurrently developed in this laboratory.[25] Specifically, mixing of **23** with ethyl trifluoropyruvate (**30**) forms the corresponding hemiacetal, which favors the formation of a six-membered cyclic borinate in the subsequent hydroboration of the alkyne with thexylborane; oxidation with trimethylamine *N*-oxide followed by a Suzuki-type cross-coupling of the resulting boronic acid ester **25** with 1-iodopropyne provided enyne **26** in appreciable yield. We are unaware of any other method that allows such a directed alkynylation to be carried out in a single operation. The elaboration of **26** into segment **29** representing the terminus of **1** and **2** was uneventful, using a regioselective alkyne silylcupration as the key step.[26,27] All other stereoisomeric building blocks of this type were prepared analogously (see the Supporting Information).

The yet missing central module was obtained by alkylation of sodium acetylide with epichlorohydrin (**31**); under the basic conditions, the primary product undergoes spontaneous deprotonation/ring opening (Scheme 5).[28] Subsequent stannylcupration of enyne **32** thus formed followed by oxidation,[9c] Wittig reaction, and reduction of the ester gave **34** in good overall yield. This product was oxidized on demand to the corresponding aldehyde, which reacted with lithiated **38** in a bora-Wittig process[29] to give the heterodimetalated



Scheme 5. a) $NaNH_2$, NH_3, acetylene, 49%; b) *n*BuLi, Bu_3SnH, CuCN, THF, 95%; c) SO_3·pyridine, DMSO, NEt_3, CH_2Cl_2, 67%; d) $Ph_3PCHCOOEt$, CH_2Cl_2, 92%; e) DIBAL-H, CH_2Cl_2, 87%; f) SO_3·pyridine, DMSO, NEt_3, CH_2Cl_2, 77%; g) **38**, lithium tetramethylpiperidinide, THF, 84%; h) (*S*,*S*)-**29**, [$PdCl_2(MeCN)_2$] (10 mol%), Ph_3As, [Ph_2PO_2][NBu_4], DMF; i) **16**, [dppf)$PdCl_2$] (10 mol%), aq. K_3PO_4, THF, 55%; j) TASF, DMF, 60%. TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate.

tetraene **35**. As anticipated, the termini of this compound can in fact be consecutively addressed: Thus a modified Stille reaction[30,31] with (*S*,*S*)-**29** was telescoped with a Suzuki coupling with iodide **16** to assemble the target framework in a single operation, which had to be carried out in the dark.

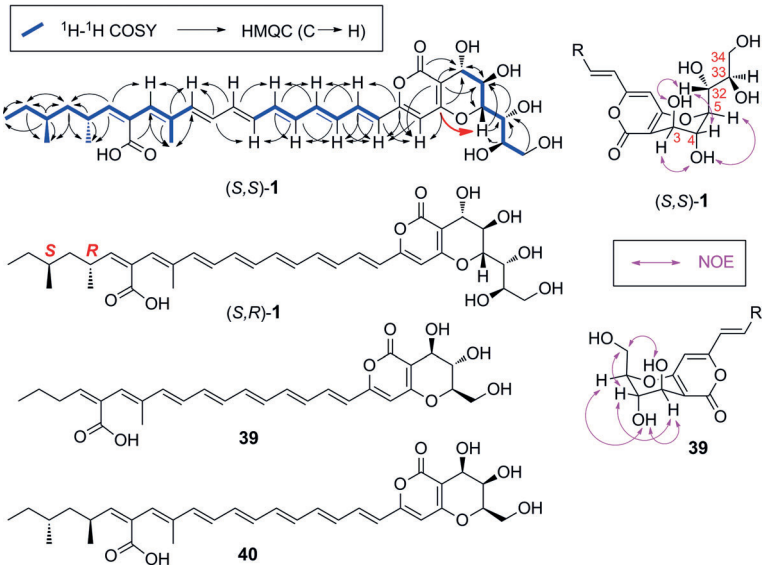


Figure 1. Confirmation of the connectivity and stereostructure of (*S*,*S*)-**1** and list of additional reference compounds; for their synthesis, see the Supporting Information.

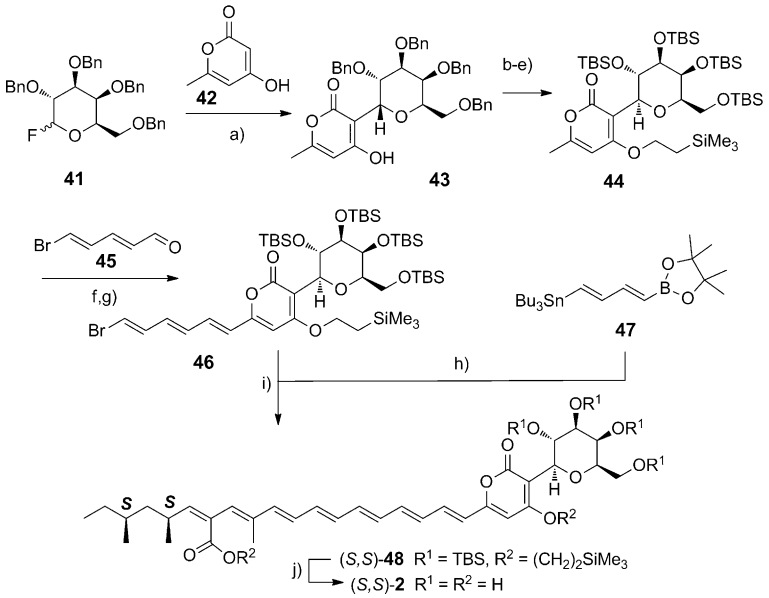
Final deprotection of (*S*,*S*)-**37** with TASF gave (*S*,*S*)-**1** as a first possible stereoisomer of the orevactaene estate.

Much to our surprise, however, only the signals of the side chain of (*S*,*S*)-**1** were in reasonable agreement with those of the natural product, whereas the spectral fingerprint of the head region deviated massively from the reported data (see the Supporting Information). The ^{1}H NMR shifts were largely off, and the ^3J couplings for the protons H3, H4, and H5 were all in the range of 3–4 Hz rather than >9 Hz as reported for **1**.[1] The differences in the ^{13}C NMR spectra were no less striking. The maximum shift differences were noted for C3 (12.0 ppm) and C33 (9.2 ppm), which can hardly be explained by stereochemical arguments. The spectra of isomer (*S*,*R*)-**1** (Figure 1) were not matching any better, which confirms that the configuration of the distal stereocluster in the tail region does not have a significant impact on the spectral features of the head group held apart by the stiff polyene chain.

Despite the configurational guarantee provided by the choice of D-arabinose as the substrate, we scrupulously confirmed the connectivity and stereostructure of synthetic (*S*,*S*)-**1** by 1D and 2D NMR spectroscopy (Figure 1): the all-*trans* substitution pattern on the pyran was unambiguously confirmed but the ring itself was found to adopt a $^1C_4$ conformation that brings all substituents in an axial rather than equatorial orientation. This striking attribute is by no means a peculiarity of the *manno*-configured entity comprised in **1**; rather, the closely related model compounds **39** and **40** derived from D-glucal and D-galactal, respectively, have the exact same spectroscopic signature.[32]

Collectively, the recorded data show that the spectral mismatch between synthetic (*S*,*S*)-**1**, (*S*,*R*)-**1**, **39**, and **40** on the one hand and putative orevactaene on the other hand cannot be attributed to stereochemical variance; rather, they must have profound structural reasons. When contemplating the different possibilities on the basis of the available data, it appeared to us that the proposed bicyclic structure of orevactaene had to be questioned altogether: in addition to the arguments arising from the coupling constants and shift differences outlined above, the original publication does not mention a long-range coupling between C6 and H5 across the ether bridge, although the isolation team had heavily relied on such means for the determination of the connectivities in the rest of the molecule;[1] importantly, however, this diagnostic coupling is unmistakable in the HMQC spectra of our synthetic samples (Figure 1, red arrow).

Under the premise that the 2-pyrone ring and the sugar segment might not be annulated as originally proposed,[1] it seems plausible that



Scheme 6. a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, MS 4 Å, 56% (α-anomer) and 6% (β-anomer); b) DBU, THF, quant.; c) 2-(trimethylsilyl)ethanol, DIAD, PPh_3, THF, 0°C→RT, 83%; d) H_2, $Pd(OH)_2$/C cat., THF; e) TBSOTf, pyridine, CH_2Cl_2, 0°C→RT, 83% (over 2 steps); f) i) LiHMDS, THF, −78°C; ii) **45**, $Sc(OTf)_3$, 63%; g) Ac_2O, Et_3N, DMAP, CH_2Cl_2; then DBU, 88%; h) (*S*,*S*)-**29**, $[PdCl_2(MeCN)_2]$ (10 mol%), Ph_3As, $[Ph_2P(O)O][NBu_4]$, DMF; i) **46**, aq. K_3PO_4, $[PdCl_2(dppf)]$ (10 mol%), THF, 57%; j) TASF, DMF, 17% (after HPLC).[36] DIAD = diisopropyl azodicarboxylate, LiHMDS = lithium hexamethyldisilazide.

orevactaene and epipyrone A are the same chemical entity. Unfortunately, this tantalizing question cannot be answered based on the literature data because their spectra had been recorded in different solvents ([D_6]DMSO versus [D_4]methanol).[1–3,5,33] Therefore, the need arose for us to prepare authentic epipyrone A (**2**). This formidable task was somewhat alleviated by the fact that the sugar contained in **2** is almost certainly galactose[2,3,5,8] and only the configuration of the chiral centers in the tail remains undefined.

The necessary C-glycosylated pyrone segment was prepared by acid-catalyzed reaction of commercial **42** with galactopyranosyl fluoride **41**[34] (Scheme 6).[8] The resulting major α-anomeric product was epimerized to the β-anomer **43**[8] prior to elaboration into alkenyl bromide **46** by deprotonation of the benzylic methyl substituent, addition of the known aldehyde **45**,[35] and elimination of the resulting secondary alcohol. The matching shorter linchpin **47** is literature-known;[9a] this amendment notwithstanding, the modularity of the synthesis blueprint paid valuable dividends at this point as the final assembly step could follow the telescope process outlined above. Final deprotection of the resulting polyene **48** gave (*S*,*S*)-**2**.[36] This endgame was repeated with all isomeric tail pieces to obtain the complete set of conceivable isomers that might represent epipyrone A (see the Supporting Information).

The NMR data compiled in the Supporting Information show that synthetic **2** is identical with putative orevactaene as well as with epipyrone A as far as can be judged from the spectra of these amphiphilic, light-sensitive, and rather unstable compounds; they confirm our hypothesis that the bicyclic structure assigned by the isolation team to the core region of orevactaene is most likely a chimera.[1] While the spectra of compounds (*S*,*S*)-**2** and (*R*,*R*)-**2** are actually both closely matching, their optical rotations in MeOH are of opposite sign, with the $[\alpha]_D$ values of (*S*,*S*)-**2** (+14.2) and epipyrone (+27.8)[3] being in no more but fair agreement; as a comparison with the reported rotational data in DMSO proved pointless,[37] however, some ambiguity remains in this regard.

Although modern spectroscopic techniques reign contemporary structure elucidation, total synthesis proved necessary to solve a riddle surrounding this unusual family of bioactive natural products.[38,39] In this particular case, two fairly discrete-looking targets were ultimately shown to be the same chemical entity. Given the size, complexity, and sensitivity of the compounds, this venture attests to the power of π-acid-catalyzed alkyne cycloisomerization and "stitching" cross-coupling chemistry using heterobimetallic linchpins that can be consecutively addressed in a single operation. Attempts at generalizing these chemical virtues are currently in progress.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cross-coupling · glycolipids · natural products · pyrones · structure determination

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Communications

Total Synthesis

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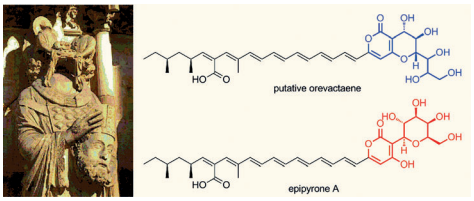
Polyunsaturated C-Glycosidic 4-Hydroxy-2-pyrone Derivatives: Total Synthesis Shows that Putative Orevactaene Is Likely Identical with Epipyrone A



The wrong head: Synthesis shows that the proposed structure of orevactaene is a chimera; rather than comprising a head group in which the sugar is annulated to a 2-pyrone, the compound is a regular β-C-glycoside and hence most likely identical with epipyrone A. A tungsten-catalyzed glycal formation, a gold-catalyzed pyrone cyclization, and a stitching assembly process using a heterobimetallic linchpin were key for solving the riddle.