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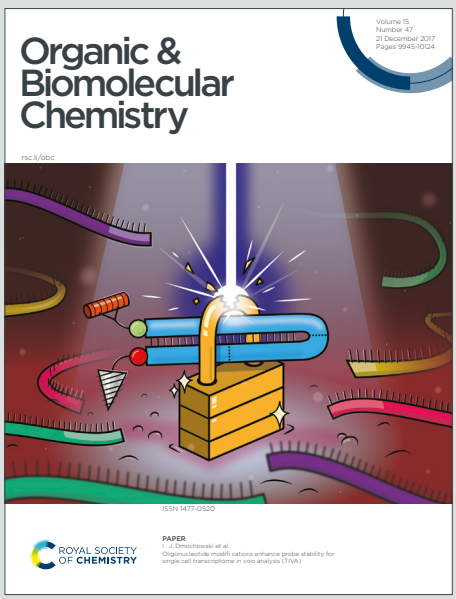

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ARTICLE

A pyridinium anionic ring-opening reaction applied to the stereodivergent syntheses of *Piperaceae* natural products †

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Abstract

A stereodivergent strategy has been devised to access the diene motif found in biologically active compounds from the *Piperaceae* family. Herein the first total syntheses of 2*E*,4*E* configured piperchabamide E (**2**) and its enantiomer (*ent*-**2**), as well as 2*E*,4*Z* configured scutifoliamide B (**3**), are narrated. The mainstay in the adopted approach is the gram-scale conversion of quaternized pyridine in a practical three-step sequence to access isomerically pure conjugated bromodiene esters 2*E*,4*E* **8** and 2*E*,4*Z* **9** by differential crystallization. Even though the developed oxidation protocol forms the basis of the entailed divergent strategy, the geometrical integrity of the involved bromodiene motive can be controlled by the choice of solvent. Thus, while oxidation of pure bromodienal 2*E*,4*Z* **7** in methanol yields equal amounts of bromodiene esters 2*E*,4*E* **8** and 2*E*,4*Z* **9**, only bromodiene ester 2*E*,4*Z* **10** is formed in isopropanol. Subseqently, capitalizing on a stereoretentive Suzuki cross-coupling and direct amidation of the corresponding esters, the featured natural products can be accessed in five and six steps, respectively. The somewhat surprising (*R*)-configured amine portion, which has been assigned to piperchabamide E (**2**), is facilitated by a Curtius rearrangement. Following this, the actual amine portion is shown to be (*S*)-configured.

Introduction

Certain members of the *Piperaceae* family have played an important role in traditional medicine since time immemorial. Thus, ancient Ayurvedic texts make references to long pepper (*Piper longum*).[1] Following the trading routes established in antiquity, the flow of goods convoyed new ideas between the East and the West. This not only established various members of the *Piper genus* as prized universal gustatory enhancers, but also shaped the notion of their efficacy as a remedy for various ailments.[2] The foundation of the causative perception has since been explored in a scientific context, identifying piperine (**1**) as a principal component of the dried fruit.[3] While the compound is initially described as tasteless upon ingestion, the bland first impression is soon taken over by a sharp and distinctly peppery aftertaste, accompanied by a burning sensation.[4] At the basis of this physiological response is the vanilloid activated nonselective cation channel TRPV1, which is a neuronal receptor and a mediator of heat-induced nociception.[5] A prominent feature of piperine (**1**) is therefore the sensory effect associated with TRPV1 agonism.[6] However, expounding on the pharmacological aspects,[7] amongst other effects, piperine (**1**) has been demonstrated to profoundly inhibit airway inflammation in a murine asthma model.[8]

In general, the alkamide phytochemicals constitute a significant and characteristic class of secondary metabolites obtained from the *Piper* genus.[1a] Yet, of particular interest to the present authors are two related structures that exemplify the rich and varied pharmacopeia of the *Piperaceae* family, highlighting the value of a well-conceived synthetic strategy to furnish the pertinent motifs. Hence, the focal point of the presented narrative are the alkamides named piperchabamide E (**2**) and scutifoliamide B (**3**) (Figure 1).[9,10]

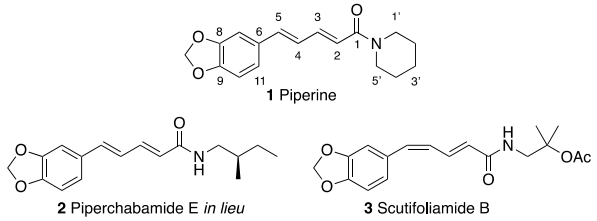

Fig. 1: Proposed structures of piperchabamide (**2**) and scutifoliamide (**3**) in relation to piperine (**1**).

Piperchabamide E (**2**) is an alkamide that closely resembles piperine (**1**) to the extent that they have the same non-amine portion in common. Consequently, the vanillin pharmacophore takes the shape of a 1,3-benzodioxolane appended to a 2*E*,4*E*-penta-2,4-dienoyl unit in the 5-position. However, instead of a piperidine ring, the compound flaunts a striking (*R*)-2-methylbutan-1-amine. This particular topology of the featured

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amine portion was assigned following an acidic hydrolysis of the natural product.[9a] Isolated from the fruit portion of *Piper chaba*, which is widespread in Southeast Asia, it has been shown that piperchabamide E (**2**) exhibits a strong and dose-dependent hepato-protective effect by inhibiting D-GalN/TNF-α-induced cell death in primary cultured mouse hepatocytes.[9] In fact, in this murine model, piperchabamide E (**2**) outperforms piperine (**1**), suggesting that the amine portion is of importance.

Deviating from the mentioned pharmacophore in terms of olefin geometry, scutifoliamide B (**3**) is an alkamide that contains a relatively rare 2*E*,4*Z*-penta-2,4-dienoyl unit. Also, the amine portion consists of an aminoethanol motif in the form of 1-amino-2-methylpropan-2-yl acetate. Isolated from the leaves of *Piper scutifolium*, the compound has demonstrated antifungal activity in an assay based on inhibition of two fungi from the genus *Cladosporium*.[10]

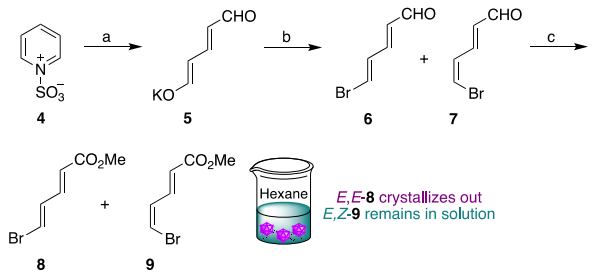
Attracted by the fact that both piperchabamide E (**2**) and scutifoliamide B (**3**) are novelties in a synthetic context, the purpose of the account is to showcase the utility of pyridinium anionic ring-opening as the means to stringently build up the entailed motifs.[11a] Traditional medicine is the origin of modern pharmacology and the diverse physiological activity scientifically documented for *Pipereceae* natural products called upon our attention.[6-10]

Results and discussion

The azomethine functionality characteristic of pyridine confers a latent reactivity on the ring system as the heteroatom significantly lowers the resonance energy.[12] The propensity to undergo nucleophilic addition is hyphenated once the orthogonal lone pair is quaternized and the adduct readily reconfigures to expose the underlying open-chained π-system. Thus, the ring-opening of quaternary pyridinium compounds leads to a conjugated diene with useful synthetic handles at each terminus.[11a] This invites further chemical elaboration and offers a potentially attractive alternative to traditional olefination protocols.[11,13]

In the case of pyridinium-1-sulfonate **4**, treatment with excess aqueous potassium hydroxide has been reported to furnish the anhydrous glutaconaldehyde potassium salt **5**.[14] Modifying the published protocol by desisting from heating the reaction mixture to 30-40 °C, but rather allowing incubation for a prolonged time at room temperature, it was possible to make improvement on both quantity and quality of the synthetic entry point. Accordingly, when performed on a 50 g-scale, the ring-opened product **5** was obtained in good yield and with high chemical purity. The outlined transformation of **4** supplied the backbone of a 3-step procedure devised to divergently deliver the conjugated motifs found in **2** and **3** (Scheme 1).

With the intent on transition metal catalysed cross-coupling to forge the union between the aromatic fixture and the alternate diene portion, the central vinyl bromide functionality was introduced under Appel conditions.[15] In this particular system the reaction takes place via a 1,6-addition/elimination pathway to afford the isomeric bromodienals 2*E*,4*E* **6** and 2*E*,4*Z* **7** in an initial 7:3 ratio, respectively. If solely the 2*E*,4*E* isomer **6** is of interest, the mixture may be isomerized to the all-*E* diene system by treatment with a catalytic amount of PTSA in diethyl ether and concomitant slow removal of the solvent. If, however, both the 2*E*,4*E* isomer **6** and the 2*E*,4*Z* isomer **7** are of interest, as was the case in the featured endeavour, the mixture may be equilibrated into an equal distribution of the two configurational isomers upon standing in hydrated chloroform.[16]



Scheme 1 Synthesis of isomeric 5-bromo-2,4-dienoates **8** and **9**. Reagents and conditions: (a) KOH (aq), –20 to 25 °C, 7 h, 68%; (b) Br_2, Ph_3P, CH_2Cl_2, 0 °C to rt, o.n. 85%; (c) (i) Oxone®, methanol, rt, 24 h; (ii) recrystallization from hexane at –20 °C, afforded **8** and **9** in 66% combined yield.

Following formation of the consigned isomeric mixture, **6** and **7** were then jointly oxidized to their corresponding methyl esters **8** and **9**, using a mild one-pot reaction consisting of Oxone® in methanol.[17] As it was assumed that the two geometric isomers would differ in their ability to aggregate via π-stacking,[18] the mixture was subjected to recrystallization from hexane. At -20 °C, the 2*E*,4*E* isomer **8** was only poorly soluble and consequently crystallized out of the solution, while the 2*E*,4*Z* isomer **9** remained in the supernatant. This therefore allowed separation of the mixture into the individual bromodiene esters.

As intended, the adjustment of oxidation level conferred an increased stability on the bromide handle, pre-empting isomerization and degradation previously observed in the antecedent aldehydes.[15b] Thus, both methyl esters **8** and **9** could be stored in a freezer under argon for over a year without any appreciable alteration. Furthermore, in all regards, i.e. synthetic preparation, purification and subsequent chemical manipulations, the dienes functionalized with an ester terminus rather than a free carboxylic acid, performed better. As a caveat, though, it must be mentioned that, the oxidative protocol employed here is not extrinsically conservative in a geometric sense. Consequently, with regard to scope and limitations, pure bromodienal 2*E*,4*Z* **7** cannot reliably be oxidized directly to pure 2*E*,4*Z* methyl ester **9**. Instead, we have found that an isomerization takes place in methanol to afford a 1:1 mixture of the two geometric esters **8** and **9**. However, when the oxidation was performed in isopropanol, pure bromodienal 2*E*,4*Z* **7** was cleanly converted to the corresponding 2*E*,4*Z* isopropyl ester **10**. The contrasting outcome is taken to signify the difference in steric requirements when the alcoholic medium acts as a nucleophile: While methanol may react with the acyl bromodiene moiety following a 1,6-addition/elimination sequence and concomitant geometric

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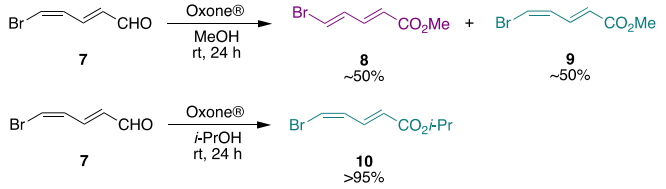
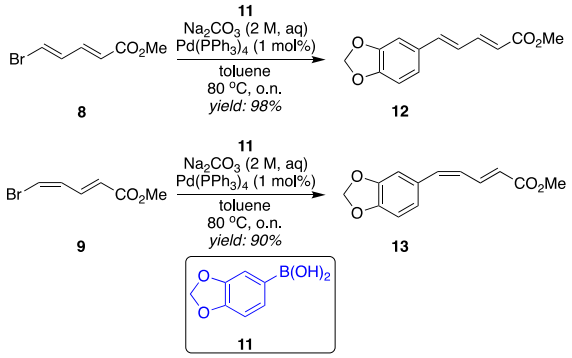
scrambling, isopropanol does clearly not embark on said pathway to any appreciable extent (scheme 2).



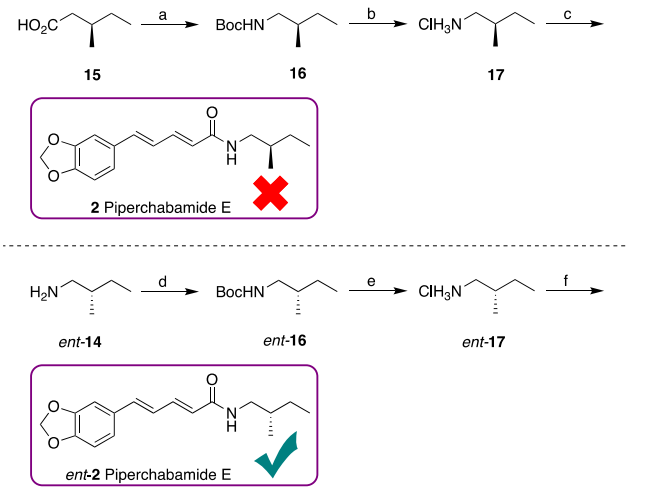
Scheme 2 Oxidation of bromodienal 2*E*,4*Z* **7** and the effect of different alcoholic media on configurational integrity.

In order to effectuate the stereodivergent strategy we have outlined for piperchabamide E (**2**) and scutifoliamide B (**3**), the crux was to identify a stereoretentive cross-coupling protocol that could faithfully reproduce the olefin geometry in both of the targeted structures. While this was not anticipated to represent a problem in terms of the 2*E*,4*E* configuration, the retention of the 2*E*,4*Z* configuration posed a somewhat more open question. Thus, π-σ-π equilibration is an immanent possibility, since, for example, Pd(0) can act as a general nucleophile in consort with a strongly Lewis acidic organometallic reagent. The result is a π-allyl complex, rather than a σ-vinyl complex, by a coordinated attack on the 1,6-conjugated system.[19] Consequently, a geometric isomerization similar to that observed during oxidation of bromodienal 2*E*,4*Z* **7** may also accompany Pd-catalysed cross-coupling on 2*E*,4*Z* methyl ester **9**. With this in mind, it was opted to take a leaf out of the Suzuki reaction protocol, using commercially available boronic acid **11** in the presence of the usual working horse catalyst, $Pd(PPh_3)_4$ (Scheme 3).[20] In both cases, cross-coupling between the mildly Lewis acidic organoboron reagent and the prenominated substrates proceeded smoothly to establish the featured structural backbones **12** and **13** of the natural products in excellent yields. Most importantly, the reactions proceeded without any observable isomerization of the involved olefin geometries as verified by evaluation of the observed coupling constants.



Scheme 3 Synthesis of isomeric 5-arylpenta-2,4-dienoates **12** and **13**.

With the intended stereodivergent aspect established, the final step in our executive strategy leading to piperchabamide E (**2**) involved direct amidation of the methyl (2*E*,4*E*)-5-arylpenta-2,4-dienoate **12** (Scheme 4). This, however, called for a concise synthesis to furnish the required amine portion, as (*R*)-2-methylbutan-1-amine **14** is not commercially available. Reflecting the practical aspects of handling the low-molecular-weight fragment, we settled on a one-pot interconversion of enantiopure carboxylic acid **15** to obtain the corresponding Boc-protected amine **16**, capitalizing on Curtius rearrangement and concomitant carbamate formation.[21] Initially, the telescoped sequence was performed with diphenyl phosphoryl azide in *tert*-butanol at 100 °C, using triethylamine as a base. Although the intermediate isocyanate could be trapped with *tert*-butanol to afford **16**, the reaction was marred by moderate yields and tedious purification to remove spent reagent together with various biproducts. Consequently, it was instead opted for a protocol wherein carboxylic acid **15** was treated with the constellation of sodium azide and Boc_2O, coaxing the desired conversion with catalytic amounts of zinc triflate and tetrabutylammonium bromide (TBAB) in THF at 40 °C.[22] A somewhat prolonged reaction time was needed to ensure complete consumption of the starting material, but in return, these conditions cleanly furnished the desired Boc-protected amine **16** in 80% yield after a straight-forward purification process. We next focused on devising a procedure for efficient removal of the Boc-protecting group in order to obtain a surrogate of the volatile amine **14** in a sufficiently pure and dry form for the final amidation step. To this end, treating **16** with 3 M HCl in cyclopentyl methyl ether for three hours and then removing the solvent under vacuum, supplied the well-behaved amine hydrochloride salt **17**.



Scheme 4. Total synthesis and subsequent reassignment of piperchabamide E to *ent*-**2**. Reagents and conditions: (a) NaN_3, Boc_2O, $Zn(OTf)_2$ (cat.), TBAB (cat.), THF, 40 °C, 120 h, 80%; (b) 3 M HCl, CPME, 0 °C to rt, 3 h, 84%; (c) Me_3Al, benzene, 0 °C to rt, 1.5 h, then **12**, rt to 80 °C, o.n., 85%; (d) Boc_2O, Et_3N, 0 °C to rt, 3 h, 90%; (e) 3 M HCl, CPME, 0 °C to rt, 3 h, 79%; (f) Me_3Al, benzene, 0 °C to rt, 1.5 h, then **12**, rt to 80 °C, o.n., 82%.

Having furnished the individual fragments professed to be featured in the natural product from *Piper chaba*, we could then undertake the last required transformation. Thus, treatment of amine hydrochloride **17** with one equivalent of trimethylaluminum generated the corresponding, oxophilic, methylchloroaluminum amide *in situ*,[23] which subsequently underwent a smooth reaction with the methyl (2*E*,4*E*)-5-arylpenta-2,4-dienoate **12** (sometimes also referred to as methyl piperate). This afford the targeted compound **2** in 18%

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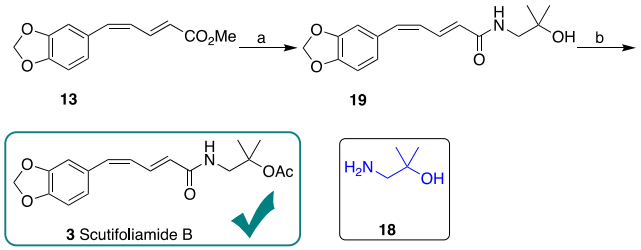
total yield over 5 steps (longest linear sequence). According to subsequent HPLC analysis, the purity of the material produced by the outlined sequence was >95%. However, while compound **2** conformed to all of the spectroscopic data provided for piperchabamide E,[9a] the recorded optical rotation deviated both in magnitude and in sign. Whereas we registered an $[\alpha]_D^{20} = -8.1$ (*c* 0.70, $CHCl_3$) for compound **2**, the published value for piperchabamide E was given as $[\alpha]_D^{20} = +18.0$ (*c* 0.72, $CHCl_3$). Following this, we concluded that the stereochemical configuration originally assigned to the amine portion found in piperchabamide E must be wrong. However, the finding may not be that surprising, since a credible biogenesis of the *Piperaceae* alkamides points to the enzymatic decarboxylation of common L-amino acids as the source of the amine portion.[27] For the proposed structure of piperchabamide E (**2**), the implication is that the appended (*R*)-2-methylbutan-1-amine **14** is derived from a nonproteinogenic precursor, which must either be L-allo-isoleucine or D-isoleucine. Even though L-allo-isoleucine has been found in dates,[28] it is by all accounts an exotic amino acid in plants. Furthermore, the biochemical pathway that leads to L-allo-isoleucine begins with L-isoleucine.[29]

Given the discussion instigated by our contrasting findings, we were obliged to prepare antipodal piperchabamide E (*ent*-**2**). However, this also clearly demonstrated the advantages of our modular approach, since we could now utilize the commercial (*S*)-2-methylbutan-1-amine *ent*-**14** as an iterative starting point. For the purpose of intercomparison with previous values obtained from optical rotation measurements, (*S*)-2-methylbutan-1-amine *ent*-**14** was converted to the Boc-protected amine *ent*-**16**. The two antipodes were found to be in good agreement on account of similar magnitude and their opposite signs. Thus, the measurements of optical rotation on Boc-protected amines **16** and *ent*-**16** gave $[\alpha]_D^{20} = -4.1$ and $+3.8$ (*c* 1.00, MeOH), respectively.

With Boc-protected amine *ent*-**16** in hand, we then embarked on the remaining two steps of the previously outlined sequence. Accordingly, the Boc-group was cleaved off, whereupon the resulting amine hydrochloride salt *ent*-**17** was treated in succession with trimethylaluminum and methyl (2*E*,4*E*)-5-arylpenta-2,4-dienoate **12** to afford compound *ent*-**2**. The redefined target, i.e. antipodal piperchabamide E (*ent*-**2**), was obtained in 18% total yield over 5 steps (longest linear sequence) and in a purity >95%, based on subsequent HPLC analysis. Compared to compound **2**, all the spectroscopic data obtained from compound *ent*-**2** were identical. In consonance with the antipodal configuration, the optical rotation recorded for compound *ent*-**2** was $[\alpha]_D^{24} = +7.9$ (*c* 0.70, $CHCl_3$). By virtue of the amassed analytical data, both with respect to identity and purity, as well as the sign of the optical rotation, we find that the structure embodying compound *ent*-**2** is in good alignment with the material isolated from *Piper chaba*.[9a] Despite the disparity concerning the magnitude of optical rotation, the sign registered for compound *ent*-**2** is compliant with piperchabamide E. Furthermore, we observed that the extended structural motif found in the prepared antipodes is unstable under certain circumstances: In particular, exposure to chloroform rapidly compromised the integrity of the analyte, as noted by visual inspection and subsequent thin-layer chromatography. The presence of trace impurities (mainly phosgene and HCl), and/or added stabilizers (such as EtOH), in chloroform, can affect samples adversely.[30] We therefore venture that the prepared compound *ent*-**2** represents piperchabamide E - i.e. the material that was isolated from *Piper chaba* is piperchabamide E (*ent*-**2**).

While applicable to purely aliphatic amines, the presence of other proximal heterofunctionalities may pose a problem to the utility of trimethylaluminum for direct amidation. Hence, for introduction of the amine portion present in scutifoliamide B (**3**), we varied the synthetic repertoire slightly in order to avoid a superfluous protection scheme in the endgame (Scheme 5). Yet, given the hard aspect of methylchloroaluminum amides, we were mindful that a softer rendition of the nitrogen nucleophile could result in geometric isomerization of the extended Michael acceptor via addition-elimination. Reacting 1-amino-2-methyl-propan-2-ol **18** with the methyl (2*E*,4*Z*)-5-arylpenta- 2,4-dienoate **13**, using sodium carbonate as a base in methanol at 80 °C furnished the desired amide **19** in good yield.[24] Most gratifyingly, we did not observe any undesired adducts or the associated configurational scrambling caused by the action of a nucleophile (solvent or reagent) on the conjugated system.



Scheme 5. Total synthesis of scutifoliamide B (**3**). Reagents and conditions: (a) Amine **17**, Na_2CO_3, MeOH, 80 °C, o.n.; (b) Ac_2O, DIPEA, DMAP (cat.), CH_2Cl_2, 0 °C to rt, o.n., 66% over two steps.

The final step to reach the natural product isolated from *Piper scutifolium* involved acetylation of the tertiary alcohol in **19**. This was achieved using acetic anhydride in dichloromethane together with ethyldiisopropylamine and a catalytic amount of DMAP. Relative to an involved protection scheme orthogonal to the reaction with trimethylaluminum, the alternative protocol introduced the pertinent amide motif in 66% yield for the two steps. Consisting of six linear steps for the complete sequence, scutifoliamide B (**3**) was obtained in an overall yield of 10% and in a purity of 95%, according to subsequent HPLC analysis.

Of note, through all of these reactions, the spectroscopic signature of the *E*,*Z*-diene configuration established for methyl (2*E*,4*Z*)-5-bromopenta-2,4-dienoate **9** remained unchanged, with coupling constants of 11.8 and 14.8 Hz for the individual *Z*- and *E*-configured alkene moieties, respectively. Also, in all respects, the compound **3** prepared by the executed strategy conformed to the data provided for the natural product.[10]

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Conclusion

A versatile pyridinium anionic ring-opening has been highlighted as the means to establish the central five carbon motif featured in a class of biologically active *Piperaceae* alkamide natural products. The enhanced configurational stability conferred on conjugated dienes at ester oxidation level formed the basis of a divergent strategy, delivering the first total syntheses of the proposed structure of piperchabamide E (**2**) and its enantiomer *ent*-**2**, as well as scutifoliamide B (**3**). Based on the presented work, we suggest the reassignment of piperchabamide E to *ent*-**2**. Capitalizing on a Suzuki cross-coupling reaction and direct amidation protocols, the targeted natural products were obtained in a short, flexible and concise manner (five and six steps, respectively). Thus, the conceived stratagem was instrumental in the explorative work, leading to the suggested reassignment of piperchabamide E as *ent*-**2**. Furthermore, the biological activity of compounds adhering to the TRPV1 pharmacophore, endorsed by piperine (**1**), makes the stringent approach a valuable contribution for functional diversification.

Experimental

General information

Unless stated otherwise, all commercially available reagents and solvents were used in the form they were supplied without any further purification. Optical rotations were measured using a 1 mL cell with a 1.0 dm path length on a Perkin Elmer 341 polarimeter. Mass spectra were recorded at 70 eV on Micromass Prospec Q or Micromass QTOF 2 W spectrometer using ESI as the method of ionization. High-resolution mass spectra were recorded at 70 eV on Micromass Prospec Q or Micromass QTOF 2W spectrometer using ESI as the method of ionization. Purity HPLC analyses were performed using a C18 stationary phase (Eclipse XDB-C18, 4.6 × 250 mm, particle size 5 µm, from Agilent Technologies, Santa Clara, CA, USA), applying the conditions stated.

Potassium (1*E*,3*E*)-5-oxopenta-1,3-dien-1-olate (5).[14] Pyridinium-1-sulfonate (**4**) (50 g, 0.314 mol, 1 equiv.) was added portionwise over 5 minutes to a solution of potassium hydroxide (71.8 g, 1.28 mol, 4.1 equiv.) in water (175 mL) at −20 °C with efficient stirring. Any large lumps that formed were broken with the aid of a glass rod against a positive pressure of argon. After complete addition of the pyridine complex, the yellow reaction mixture was stirred for one hour before the cooling bath was removed. The flask was stirred for six hours at room temperature and during this time, the reaction mixture took on an increasingly dark brown colour. The flask was then cooled to 0 °C, the suspension was filtrated, the crude, solid product was washed with acetone (4 × 40 mL) and then the material was dried under vacuum overnight. The crude product was added to methanol (700 mL) and activated charcoal (5 g) and refluxed with efficient stirring for 15 minutes before the contents of the flask was quickly subjected to a hot filtration. Additional boiling in methanol (~100 mL × 2) was used to wash the remaining solid material in the filtration funnel. The filtrate was cooled to room temperature and concentrated in vacuo until a thick slurry was obtained. The solid was collected in a Büchner funnel using vacuum filtration, washed with acetone (5 × 20 mL) and dried overnight under high vacuum to afford a light brown glutaconaldehyde potassium salt **5**. Yield: 29.1 g, 68%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, *J* = 9.2 Hz, 2H), 7.04 (t, *J* = 13.1 Hz, 1H), 5.11 (dd, *J* = 13.1, 9.2 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 184.4, 159.8, 106.2.

(2*E*,4*E*)-5-Bromopenta-2,4-dienal (6) and (2*E*,4*Z*)-5-bromopenta-2,4-dienal (7).[16] Triphenylphosphine (11.2 g, 42.6 mmol, 1.35 equiv.) was dissolved in dichloromethane (150 mL) and cooled to 0 °C. A solution of bromine (2.10 mL, 41.0 mmol, 3.12 g/mL at 25 °C, 1.3 equiv.) was dissolved in dichloromethane (38 mL) and the solution was added dropwise with efficient stirring. (If there was a persistent reddish-brown colour after complete addition of the bromine solution, additional triphenylphosphine was added in small portions until the colour disappeared). Potassium (1*E*,3*E*)-5-oxopenta-1,3-dien-1-olate (**5**) (4.3 g, 31.6 mmol, 1 equiv.) was then added in one portion and the reaction mixture was stirred overnight, allowing it to attain room temperature. The reaction mixture was then filtered through a pad of silica gel, the flask was washed with fresh dichloromethane, with the washings filtered through the silica gel pad and then the filtrate was concentrated *in vacuo*. The material thus obtained was purified by column chromatography (SiO_2, 10% Et_2O in hexane) to give a mixture of (2*E*,4*E*)-5-bromopenta-2,4-dienal (**6**) and (2*E*,4*Z*)-5-bromopenta-2,4-dienal (**7**). Yield: 4.3 g, 85%. [NB! When only one isomer was required, separation was also achieved by column chromatography (SiO_2, 10% Et_2O in hexane)].

*(2E,4E)-5-Bromopenta-2,4-dienal (**6**)*. Colorless oil; Rf = 0.18 (10% Et_2O in hexane, $KMnO_4$-stain); ^{1}H NMR (600 MHz, C_6D_6); 9.19 (dd, J = 7.7, 2.2 Hz, 1H), 6.24 – 6.12 (m, 1H), 6.07 – 5.95 (m, 1H), 5.94 – 5.81 (m, 1H), 5.72 – 5.57 (m, 1H). ^{13}C{^{1}H} (151 MHz, C_6D_6) NMR δ 191.9, 146.6, 135.6, 132.1, 118.7.

*(2E,4Z)-5-Bromopenta-2,4-dienal (**7**)*. Colorless oil; Rf = 0.24 (10% Et_2O in hexane, $KMnO_4$-stain); ^{1}H NMR (600 MHz, C_6D_6); δ 9.15 (d, *J* = 7.8 Hz, 1H), 6.87 (dd, *J* = 15.6, 10.6 Hz, 1H), 5.88 (dd, *J* = 10.4, 7.3 Hz, 1H), 5.84-5.76 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, C_6D_6) δ 192.3, 144.1, 134.9, 130.9, 117.4.

Methyl (2*E*,4*E*)-5-bromopenta-2,4-dienoate (8) and methyl (2*E*,4*Z*)-5-bromopenta-2,4-dienoate (9). A mixture of *E,E*- and *E,Z*-bromodienal **6** and **7** (3.3 g, 20.5 mmol) was dissolved in dry methanol (200 mL) and then potassium peroxymonosulfate (9.45 g, 30.7 mmol, 1.50 equiv.) was added in one portion. The flask was flushed with argon and stirred 24 hours (Note that TLC analysis can be deceiving in this case as starting material will disappear after a few hours and reappear after work-up – likely due to acetal formation). The flask was then placed on a rotary evaporator in order to remove most of the methanol until a slurry was obtained. Next, ethyl acetate (50 mL) was added, rapid stirring was turned on and an aqueous 1 M solution of HCl was added carefully until all the salts had dissolved. The aqueous phase was extracted with ethyl acetate (5 x 50 mL), the combined organic phase was dried (Na_2SO_4), filtrated and concentrated *in vacuo*. The crude material was purified by column chromatography (SiO_2, 10% Et_2O in hexane, $KMnO_4$-

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stain) to give a mixture of geometric isomers. The fractions containing product were combined and the flask was placed on a rotary evaporator in order to remove approximately 80% of the solvent volume. The flask was then placed in a -20 °C freezer which lead to the crystallization of the *E,E*-isomer while the *E,Z*-isomer remained in solution. The supernatant was carefully transferred into a new flask and the crystals of the *E,E*-isomer were washed with ice-cold hexane (2 × 5 mL). This process gave pure methyl (2*E*,4*E*)-5-bromopenta-2,4-dienoate (**8**) (1.50 g, 7.85 mmol) and methyl (2*E*,4*Z*)-5-bromopenta-2,4-dienoate (**9**) (1.10 g, 5.76 mmol), the latter contaminated by approximately ~7% of the former-mentioned *E,E*-isomer. This process may be repeated for the *E,Z*-isomer if necessary. Combined yield: 2.6 g, 66%; Rf = 0.39 (10% Et_2O in hexane, $KMnO_4$-stain). Both isomers co-elute on TLC under these conditions.

*Methyl (2E,4E)-5-bromopenta-2,4-dienoate (**8**)*. Needle-like, colorless, crystals; Mp.: 46.5–47.0 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 15.4, 10.4 Hz, 1H), 6.93–6.67 (m, 2H), 5.92 (d, *J* = 15.3 Hz, 1H), 3.74 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.1, 141.4, 135.5, 121.9, 118.1, 51.9.

*Methyl (2E,4Z)-5-bromopenta-2,4-dienoate (**9**)*. Colorless oil; ^{1}H NMR (400 MHz, MeOD) δ 7.58 (ddd, *J* = 15.5, 10.7, 1.1 Hz, 1H), 6.92 (ddd, *J* = 10.7, 7.2, 0.8 Hz, 1H), 6.77 (dt, *J* = 7.3, 0.9 Hz, 1H), 6.18 (d, *J* = 15.5 Hz, 1H), 3.76 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, MeOD) δ 167.1, 138.9, 130.3, 124.3, 116.5, 50.9.

Isopropyl (2*E*,4*Z*)-5-bromopenta-2,4-dienoate (10). (2*E*,4*Z*)-5-Bromopenta-2,4-dienal (**7**) (561 mg, 3.38 mmol, 1 equiv.), which had been freshly purified from an equilibrated mixture of geometric isomers[16] by flash column chromatography, was dissolved in dry isopropanol (35 mL). Potassium peroxymonosulfate (1.61 g, 5.23 mmol, 1.5 equiv.) was added in one portion and the reaction mixture was stirred for 24 hours. The flask was then placed on a rotary evaporator in order to remove most of the isopropanol and a slurry was obtained. Next, ethyl acetate (10 mL) was added, rapid stirring was turned on and an aqueous 1 M solution of HCl was added carefully until all of the salts had dissolved. The aqueous phase was extracted with ethyl acetate (5 × 10 mL), the combined organic phase was dried (Na_2SO_4), filtrated and concentrated *in vacuo*. The crude material was purified by column chromatography (SiO_2, 6% Et_2O in hexane, $KMnO_4$-stain) to give isopropyl ester **10** as a colorless oil. Yield: 589 mg, 77%; Rf = 0.37 (6% Et_2O in hexane, $KMnO_4$-stain); ^{1}H NMR (400 MHz, MeOD) δ 7.55 (ddd, *J* = 15.5, 10.7, 1.1 Hz, 1H), 6.91 (ddd, *J* = 10.7, 7.2, 0.8 Hz, 1H), 6.75 (d, *J* = 7.2 Hz, 1H), 6.14 (dt, *J* = 15.5, 0.8 Hz, 1H), 5.06 (hept, *J* = 6.2 Hz, 1H), 1.28 (d, *J* = 6.3 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, MeOD) δ 167.5, 139.9, 131.8, 126.5, 117.6, 69.4, 22.1; Exact mass calculated for $C_8H_{11}BrNaO_2$ $[M+Na]^+$ m/z 240.9834, found 240.9835.

Methyl (2*E*,4*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)penta-2,4-dienoate (12).[25] A flask was charged with benzo[*d*][1,3]dioxol-5-ylboronic acid (**11**) (208 mg, 1.26 mmol, 1.20 equiv.), methyl (2*E*,4*E*)-5-bromopenta-2,4-dienoate (**8**) (200 mg, 1.05 mmol, 1.00 equiv.), 2.0 M Na_2CO_3 (3.3 mL) and toluene (5.5 mL). The flask was evacuated and vented with argon and then $Pd(PPh_3)_4$ (12.2 mg, 12.6 µmol, 1.0 mol%) was added. The flask was again evacuated and vented with argon (3×) and then the reaction mixture was heated to 80 °C and stirred overnight. After completion, the reaction mixture was cooled to room temperature, quenched by the addition of saturated aqueous NH_4Cl (25 mL) and extracted with Et_2O (5 × 20 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo*. The crude was dissolved in a minimal amount of CH_2Cl_2 (not significantly soluble in the solvent used for column chromatography) and applied to column chromatography for purification (SiO_2, 10% EtOAc in hexane, $KMnO_4$ stain) to afford the known methyl (2*E*,4*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)penta-2,4-dienoate (**12**). Yield: 238 mg, 98%; Rf = 0.52 (20% EtOAc in heptane, $KMnO_4$ stain); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.99 (d, *J* = 1.7 Hz, 1H), 6.91 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.85 – 6.75 (m, 2H), 6.70 (dd, *J* = 15.4, 10.8 Hz, 1H), 5.98 (s, 2H), 5.95 (d, *J* = 15.3 Hz, 1H), 3.76 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.7, 148.7, 148.4, 145.1, 140.4, 130.7, 124.6, 123.1, 120.1, 108.7, 106.0, 101.5, 51.7.

Methyl (2*E*,4*Z*)-5-(benzo[*d*][1,3]dioxol-5-yl)penta-2,4-dienoate (13).[26] A flask was charged with benzo[*d*][1,3]dioxol-5-ylboronic acid (**11**) benzo[*d*][1,3]dioxol-5-ylboronic acid (**11**) (208 mg, 1.26 mmol, 1.20 equiv.), methyl (2*E*,4*Z*)-5-bromopenta-2,4-dienoate (**9**) (200 mg, 1.05 mmol, 1.00 equiv.), 2.0 M Na_2CO_3 (3.3 mL) and toluene (5.5 mL). The flask was evacuated and vented with argon and then $Pd(PPh_3)_4$ (12.2 mg, 12.6 µmol, 1.0 mol%) was added. The flask was again evacuated and vented with argon (3×) and then the reaction mixture was heated to 80 °C and stirred overnight. After completion, the reaction mixture was cooled to room temperature, quenched by the addition of saturated aqueous NH_4Cl (25 mL) and extracted with Et_2O (5 × 20 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo*. The crude was dissolved in a minimal amount of CH_2Cl_2 (not significantly soluble in the solvent used for column chromatography) and applied to column chromatography for purification (SiO_2, 5→15% EtOAc in hexane, $KMnO_4$ stain) to give known methyl (2*E*,4*Z*)-5-(benzo[*d*][1,3]dioxol-5-yl)penta-2,4-dienoate (**13**). Yield: 219 mg, 90%; Rf = 0.54 (20% EtOAc in heptane, $KMnO_4$ stain); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (ddd, *J* = 15.3, 11.8, 1.2 Hz, 1H), 6.84–6.83 (m, 1H), 6.83–6.80 (m, 2H), 6.70 (d, *J* = 11.3 Hz, 1H), 6.32–6.18 (m, 1H), 6.01 (dt, *J* = 15.3, 0.8 Hz, 1H), 5.99 (s, 2H), 3.75 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.7, 148.0, 147.8, 140.7, 137.7, 130.6, 126.4, 123.8, 122.9, 109.4, 108.6, 101.4, 51.7.

***tert*-Butyl (*R*)-(2-methylbutyl)carbamate (16).** (*R*)-3-Methylpentanoic acid **15** (630 mg, 5.42 mmol, 1.00 equiv.), NaN_3 (704 mg, 10.8 mmol, 2.00 equiv.), TBAB (157 mg, 0.488 mmol, 9 mol%) and $Zn(OTf)_2$ (39.4 mg, 0.108 mmol, 2 mol%) were added in succession to a flame-dried flask under argon. The flask was evacuated and vented with argon (3×) and THF (27 mL) was added. The reaction mixture was heated to 40 °C, and then di-*tert*-butyl dicarbonate (1.40 mL, 6.09 mmol, 0.95 g/mL at 25 °C, 1.10 equiv.) was added dropwise via cannula. The reaction mixture was stirred for 120 hours at 40 °C, cooled to room temperature, quenched by the addition of a 10% aqueous solution of $NaNO_2$ (~10 mL) and then the reaction mixture was stirred for 30 minutes. NaCl (~5 grams) was added to the flask,

the organic phase was separated, and the aqueous phase extracted with diethyl ether (4 × 30 mL). The combined organic phase was dried (Na_2SO_4), filtrated and concentrated *in vacuo*. The crude material thus obtained was purified by column chromatography (SiO_2, 10 to 15% EtOAc in hexane, $KMnO_4$-stain) to give *tert*-butyl (*R*)-(2-methylbutyl)carbamate (**16**) as a clear oil. Yield: 813 mg, 80%; Rf = 0.39 (15% EtOAc in hexane. $KMnO_4$-stain); $[\alpha]_D^{20} = -4.1$ (c 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (br s, 1H), 3.06 (dd, *J* = 13.6, 5.8 Hz, 1H), 2.91 (dd, *J* = 13.7, 7.1 Hz, 1H), 1.60–1.30 (m, 2H), 1.44 (s, 9H), 1.19–1.07 (m, 1H), 0.93 – 0.83 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.3, 79.1, 46.4, 35.4, 28.6, 27.0, 17.2, 11.4; Exact mass calculated for $C_{10}H_{21}NNaO_2$ $[M+Na]^+$ m/z 210.1463, found 210.1464.

***tert*-Butyl (*S*)-(2-methylbutyl)carbamate (*ent*-16).** (*S*)-(-)-2-methylbutylamine *ent*-**14** (1.00 g, 1.36 mL, 11.5 mmol, 0.738 g/mL, 1.00 equiv.) was dissolved in dichloromethane (16 mL) was cooled to 0 °C. Triethylamine (2.32 g, 3.20 mL, 22.9 mmol, 0.726 g/mL, 2.00 equiv.) was added followed by the dropwise addition of di-*tert*-butyl dicarbonate (2.75 g, 2.9 mL, 12.6 mmol, 0.95 g/mL, 1.10 equiv.). After complete addition, the reaction mixture was allowed to warm to room temperature and stirred until deemed complete by TLC analysis (3 hours). The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic phase was dried (Na_2SO_4), filtrated and concentrated *in vacuo* to give the *tert*-butyl (*S*)-(2-methylbutyl)carbamate (*ent*-**16**) as a clear oil. Yield: 1.67 g, 90%; Rf = 0.39 (15% EtOAc in hexane. $KMnO_4$-stain); $[\alpha]_D^{20} = +3.8$ (c 1.00, MeOH); The recorded spectra match those cited for (*R*)-(2-methylbutyl)carbamate (**16**).

(*R*)-2-Methylbutan-1-amine hydrochloride (17). A flask was charged with Boc-protected amine **16** (200 mg, 1.07 mmol, 1.00 equiv.) and cooled to 0 °C. A solution of 3M HCl in CPME (5.4 mL, 16.0 mmol, 15.0 equiv.) was added in a dropwise manner. The cooling bath was removed after 10 minutes, the reaction mixture was allowed to warm to room temperature and then stirred until no starting material was observed based on TLC analysis (~3 hours). The bulk of solvent was removed under a stream of nitrogen and then further concentrated in vacuo. The solid material thus obtained was purified by trituration with hexane (3 × 5 mL) and then dried under vacuum to yield (*R*)-2-methylbutan-1-amine hydrochloride (**17**) as a white salt. Yield 111 mg, 84%; $[\alpha]_D^{20} = +0.43$ (c 1.00,MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (br s, 3H), 2.71 (dd, *J* = 12.6, 6.1 Hz, 1H), 2.55 (dd, *J* = 12.6, 7.7 Hz, 1H), 1.72–1.59 (m, 1H), 1.47–1.34 (m, 1H), 1.20–1.06 (m, 1H), 0.90 (d, *J* = 6.8 Hz, 1H), 0.85 (t, *J* = 7.4 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 44.0, 32.5, 26.1, 16.6, 10.8; $C_5H_{14}N$ $[M+H]^+$ m/z 88.1121, found 88.1121.

(*S*)-2-Methylbutan-1-amine hydrochloride (*ent*-17). A flask was charged with Boc-protected amine *ent*-**16** (1.00 g, 5.35 mmol, 1.00 equiv.) and cooled to 0 °C. A solution of 3M HCl in CPME (26.5 mL, 80.0 mmol, 15.0 equiv.) was added in a dropwise manner. The cooling bath was removed after 10 minutes, the reaction mixture was allowed to warm to room temperature and then stirred until no starting material was observed based on TLC analysis (~3 hours). The bulk of solvent was removed under a stream of nitrogen and then further concentrated in vacuo. The solid material thus obtained was purified by trituration with hexane (3 × 25 mL) and then dried under vacuum to yield (*S*)-2-methylbutan-1-amine hydrochloride (*ent*-**17**) as a white salt. Yield 521 mg, 79%; $[\alpha]_D^{20} = -0.55$ (c 1.00, MeOH). The recorded spectra match those cited for (*R*)-2-methylbutan-1-amine hydrochloride (**17**).

(2*E*,4*E*)-5-(Benzo[*d*][1,3]dioxol-5-yl)-*N*-((*R*)-2-methylbutyl)penta-2,4-dienamide (2).[9a] To a suspension of (*R*)-2-methylbutan-1-amine hydrochloride **17** (16.7 mg, 0.135 mmol, 2.00 equiv.) in benzene (0.14 mL) was carefully added trimethylaluminum (67.5 μL, 0.135 mmol, 2 M in toluene) at 0 °C. After complete addition, the reaction mixture was allowed to warm to room temperature and stirred for 1.5 hour. A solution of methyl (2*E*,4*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)penta-2,4-dienoate (**12**) (15 mg, 64.6 μmol, 1.00 equiv.) in benzene (0.75 mL) was then added the resulting mixture was stirred for 80 °C overnight. The reaction mixture was cooled to room temperature and slowly quenched with the addition of aqueous 5% HCl. The organic layer was separated, and the aqueous layer extracted with ethyl acetate (4 × 1 mL). The combined organic phase was dried (Na_2SO_4), concentrated in vacuo and purified by column chromatography (SiO_2, 20 to 40% EtOAc in hexane, $KMnO_4$-stain) to yield (2*E*,4*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)-*N*-((*R*)-2-methylbutyl)-penta-2,4-dienamide (**2**) as a white solid. Yield: 16 mg, 85%; Rf = 0.27 (40% EtOAc in hexane, $KMnO_4$-stain); $[\alpha]_D^{24} = -8.1$ (c 0.70, $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6) δ 7.67 (dd, *J* = 14.8, 11.0 Hz, 1H), 6.85 (d, *J* = 1.4 Hz, 1H), 6.59–6.53 (m, 3H), 6.43 (d, *J* = 15.5 Hz, 1H), 5.61 (dd, *J* = 14.9, 0.8 Hz, 1H), 5.26 (s, 2H), 3.23 (dd, *J* = 13.3, 6.2 Hz, 1H), 3.10 (dd, *J* = 13.3, 7.2 Hz, 1H), 1.43 (dq, *J* = 13.3, 6.7 Hz, 1H), 1.33–1.24 (m, 1H), 1.07–0.96 (m, 1H), 0.82 (t, *J* = 7.4 Hz, 3H), 0.78 (d, *J* = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, C_6D_6) δ 165.4, 148.7, 148.6, 140.9, 138.6, 131.5, 125.3, 124.4, 122.9, 108.7, 106.1, 101.2, 45.3, 35.6, 27.3, 17.3, 11.5; Exact mass calculated for $C_{17}H_{21}NNaO_3$ $[M+Na]^+$ m/z 310.1413, found 310.1414. The purity was determined by HPLC analysis (Eclipse XDB-C18, MeOH/H_2O 60:40, 1.0 mL/min, 254 nm) t_R = 23.99, >95%.

(2*E*,4*E*)-5-(Benzo[*d*][1,3]dioxol-5-yl)-*N*-((*S*)-2-methylbutyl)penta-2,4-dienamide (*ent*-2) - Piperchabamide E (*ent*-2).[9a] To a suspension of (*S*)-2-methylbutan-1-amine hydrochloride *ent*-**17** (16.7 mg, 0.135 mmol, 2.00 equiv.) in benzene (0.14 mL) was carefully added trimethylaluminum (67.5 μL, 0.135 mmol, 2 M in toluene) at 0 °C. After complete addition, the reaction mixture was allowed to warm to room temperature and stirred for 1.5 hour. A solution of methyl (2*E*,4*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)penta-2,4-dienoate (**12**) (15 mg, 64.6 μmol, 1.00 equiv.) in benzene (0.75 mL) was then added the resulting mixture was stirred for 80 °C overnight. The reaction mixture was cooled to room temperature and slowly quenched with the addition of aqueous 5% HCl. The organic layer was separated, and the aqueous layer extracted with ethyl acetate (4 × 1 mL). The combined organic phase was dried (Na_2SO_4), concentrated in vacuo and purified by column chromatography (SiO_2, 20 to 40% EtOAc in hexane, $KMnO_4$-stain) to yield (2*E*,4*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)-*N*-((*S*)-2-methylbutyl)-penta-2,4-dienamide (*ent*-**2**) - piperchabamide E

(*ent*-**2**) as a white solid. Yield: 15.2 mg, 85%; Rf = 0.27 (40% EtOAc in hexane, $KMnO_4$-stain); $[\alpha]_D^{24} = +7.9$ (*c* 0.70, $CHCl_3$). The recorded spectra match those cited for (2*E*,4*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)-*N*-((*R*)-2-methylbutyl)penta-2,4-dienamide (**2**); The purity was determined by HPLC analysis (Eclipse XDB-C18, MeOH/H_2O 60:40, 1.0 mL/min, 254 nm) t_R (major) = 24.03 and t_R (minor) = 25.53, >95%.

1-((2*E*,4*Z*)-5-(benzo[*d*][1,3]dioxol-5-yl)penta-2,4-dienamido)-2- methylpropan-2-yl acetate (3) – Scutifoliamide B (3).[10] Methyl ester **12** (30 mg, 0.129 mmol, 1.00 equiv.) was dissolved in methanol (0.13 mL) and 1-amino-2- methylpropan-2-ol **18** (62.6 µL, 0.646 mmol, 0.92 g/mL at 25 °C, 5.00 equiv.) and then Na_2CO_3 (13.7 mg, 0.129 mmol, 1.00 equiv.) was added. The reaction flask was flushed with argon, capped and then heated to 80 °C overnight. The flask was cooled, and the volatiles were removed under a stream of argon. The crude ((2*E*,4*Z*)-5-(benzo[*d*][1,3]dioxol-5-yl)-*N*-(2-hydroxy-2-methylpropyl)penta-2,4-dienamide **19** was taken up in a minimal amount of ethyl acetate and loaded directly onto a short plug of silica gel – eluting with 70% EtOAc/1% MeOH in hexane (Rf = 0.53; KMnO4-stain). The fractions containing the product were combined and concentrated *in vacuo*. The material thus obtained (29 mg) was dissolved in dichloromethane (0.3 mL) and cooled to 0 °C. Ethyldiisopropylamine (25.7 µL, 0.150 mmol, 0.757 g/mL at 25 °C, 1.50 equiv.), DMAP (1.22 mg, 10.0 µmol, 10 mol%) and acetic anhydride (12.3 µL, 0.130 mmol, 1.08 g/mL at 25 °C, 1.30 equiv.) were added in succession and the reaction mixture was allowed to warm up to room temperature and then stirred overnight. The reaction was cooled to 0 °C and quenched by the addition of saturated aqueous NaH_2PO_4 (0.3 mL) and ethyl acetate (0.3 mL). The organic phase was separated, and the aqueous phase extracted with ethyl acetate (4 × 0.3 mL). The combined organic phase was dried (Na_2SO_4), filtrated and concentrated *in vacuo*. The crude material thus obtained was purified by column chromatography (SiO_2, 40% EtOAc in hexane) to give scutifoliamide B (**3**) as a slightly yellow oil. Yield: 28 mg, 66% over two steps; Rf = 0.12 (40% EtOAc in hexane, $KMnO_4$-stain); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (ddd, *J* = 14.8, 11.8, 1.1 Hz, 1H), 6.87–6.74 (m, 3H), 6.64 (d, *J* = 11.3 Hz, 1H), 6.25 (t, *J* = 11.8 Hz, 1H), 6.03 (d, *J* = 14.8 Hz, 1H), 5.97 (s, 2H), 3.59 (d, *J* = 6.0 Hz, 2H), 2.02 (s, 3H), 1.45 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.9, 166.1, 147.8, 147.5, 137.1, 136.3, 130.6, 126.3, 125.7, 123.5, 109.3, 108.4, 101.2, 82.4, 48.1, 24.1, 22.4; Exact mass calculated for $C_{18}H_{21}NNaO_5$ $[M+Na]^+$ m/z 354.1311, found 354.1312; The purity was determined by HPLC analysis (Eclipse XDB-C18, MeOH/H_2O 60:40, 1.0 mL/min, 254 nm) t_R (minor) = 13.37 and t_R (major) = 14.16, 95%.

Author contributions

The authors contributed equally.

Conflicts of interest

There are no conflicts to declare.

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The central motif found in biologically active compounds from the *Piperaceae* family has been obtained by a stereodivergent strategy. To this end, the utility of a pyridinium anionic ring-opening reaction was used as the means to stringently tackle the entailed isomeric dienes 2*E*,4*E* **6** and 2*E*,4*Z* **7**. Herein we report the first total syntheses of piperchabamide E (**2**) and its enantiomer (*ent*-**2**), as well as 2*E*,4*Z* configured scutifoliamide B (**3**). Following our analysis, the flexible strategy allowed the reassignment of piperchabamide E (**2**) to its enantiomer (*ent*-**2**).