Collective Syntheses of Icetexane Natural Products Based on Biogenetic Hypotheses

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Abstract: A divergent synthesis of ten members of icetexane natural products based on a proposed biogenetic cationic ring expansion of a reduced carnosic acid derivative is described. Among these members, (+)-salvicanol, (−)-cyclocoulterone, (−)-coulterone, (−)-obtusinone D and (−)-obtusinone E have been synthesized for the first time. In addition, the hypothesis for the non-enzymatic biogenesis of benzo[1,3]dioxole natural products has been further experimentally investigated. Additional experimental evidence for the abiotic formation of the methylenedioxy unit is provided, as photolysis of the quinone (+)-komaroviquinone resulted in the formation of the [1,3]dioxole-containing natural product (−)-cyclocoulterone and of (+)-komarovispirone.

Introduction

Terpenes display an extraordinary wealth of fascinating chemical structures, which provided inspiration for chemists over decades.[1] The understanding and development of cyclization reaction cascades[2], cationic rearrangements[3] or the mechanism of C–H oxidation[4] greatly influenced science, from reaction mechanisms to biosynthesis. The methylenedioxy bridged phenol unit (benzo[1,3]dioxole) is frequently found in many compounds,[5] including commercially important compounds such as the fragrances piperonal and helional®, or drugs such as ecteinascidin 743 or etoposide (**Figure 1**). Consequently, the biosynthesis of this important moiety has been investigated for decades *via* chemical, enzymatic and genetic approaches. [6]

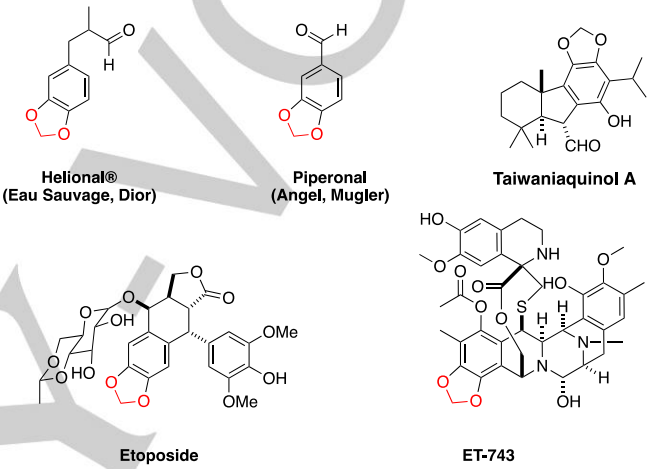
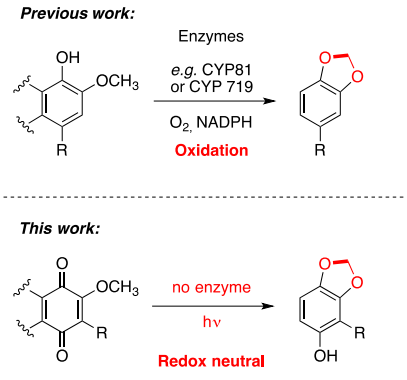


Figure 1. Terpenoids featuring the benzo[1,3]dioxole unit, including those with commercial interest.

In a landmark study published in 1962, Sir Derek Barton reported experimental evidence that the origin of the benzo[1,3]dioxole unit found in the alkaloid haemanthamine resides in a monomethyl-catechol unit, and he postulated that this transformation proceeds *via* an oxidative process. [7] This hypothesis has been substantiated by many experiments, and in recent years, the involvement of cytochrome P450 enzymes in the *oxidative cyclization* has been unequivocally demonstrated for several natural products[6] (Scheme 1, top). In the context of taiwaniaquinol A, we have previously identified an *alternative pathway* to benzo[1,3]dioxole formation that is (a) redox neutral, (b) light mediated, and most importantly (c) without the involvement of any enzymes (Scheme 1, bottom). [8]



Scheme 1. Biogenesis of benzo[1,3]dioxole natural products.

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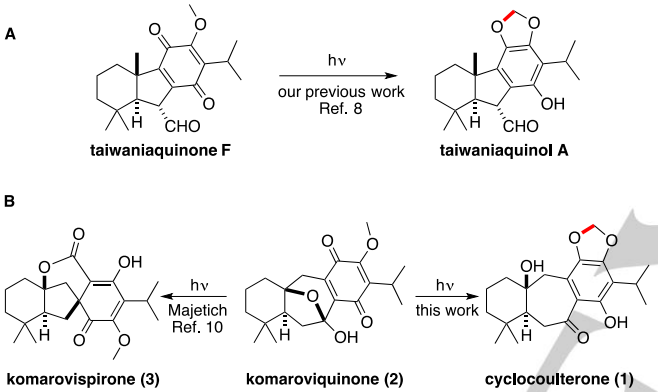
In this study, we present (1) evidence further corroborating this abiotic hypothesis *via* the preparation of two benzo[1,3]dioxole natural products in the chemical laboratory, and describe a model study aimed at elucidating mechanistic details. In addition, we investigated potential routes for the biogenesis of icetexane terpenes, and provide (2) the first experimental evidence for the abiotic formation of the tertiary OH group during the ring expansion from the abietane to the icetexane family. Finally, (3) the abiotic formation of the complex C_{40} dimers, obtusinone D and E is reported, and their configuration is reassigned. Overall, the first preparation in synthetic form of five natural products is reported, *i.e.* (+)-salvicanol, (–)-cyclocoulterone, (–)-coulterone, (–)-obtusinone D and (−)-obtusinone E, and alternative approaches for the preparation of komaroviquinone, komarovispirone, brussonol, przewalskin E and demethylsalvicanol quionone are presented in this publication.



Scheme 2. Remote C–H functionalization of taiwaniaquinone F and komaroviquinone.

In our previous study, we reported the photolysis of taiwaniaquinone F to taiwaniaquinol A (Scheme 2, **A**). [8] We proposed a hypothesis where such a methylenedioxy bridge bearing a 1,2,4-hydroxylated aryl moiety can be biosynthetically generated *via* a light promoted remote C−H activation. Regarding the biosynthesis of this structural unit, this postulate would be complementary to the well-accepted and established cytochrome P450 mechanism[6] to produce the methylenedioxy bridge, especially in the plant kingdom where the use of light as a source of energy is omnipresent. Therefore, the first goal of this study consisted in demonstrating that the previously discovered photolysis of taiwaniaquinone F can also be applied to additional substrates in order to emphasize the generality of this transformation in Nature. Therefore, we proposed that the complex benzo[1,3]dioxole derivative cyclocoulterone (**1**) [9] (Scheme 2, **B**) could be generated from komaroviquinone (**2**) [9] *via* such an abiotic ring formation reaction as postulated above. In support of the biogenetic hypothesis of this transformation, both cyclocoulterone (**1**) and komaroviquinone (**2**) were isolated from the same plant (*Dracocephalum komarovi*), corroborating a possible biogenetic connection between both natural products. [9] A previous report of Majetich and co-workers describes the photolysis of komaroviquinone (**2**) in cyclohexane, which furnished komarovispirone (**3**) in high yield.[10] However, these authors detected an unknown product in low yield, which however was not characterized at the time. We expected that the use of the conditions developed for the photolysis of taiwaniaquinone F would turn the course of the photolysis of komaroviquinone (**2**) in favor of the generation of cyclocoulterone (**1**). If successful, this abiotic, non-enzymatic transformation of komaroviquinone (**2**) to cyclocoulterone (**1**) would further substantiate the abiotic hypothesis of benzo[1,3]dioxoles. In order to test this hypothesis, first the icetexane precursor **2** had to be prepared in synthetic form.

Results and Discussion

Investigation of the Ring Expansion in Icetexane Biogenesis. Icetexanes constitute a variety of diterpenoids isolated from diverse plant sources, in particular from the *Labiatae* family. [11] These compounds exhibit a unique carbon skeleton consisting of a 6-7-6 tricyclic core structure (Figure 2). The systematic name 9(10→20)-abeo-abietane given to icetexanes indicates an abietane precursor such as **4** could be involved in biosynthetic origin of icetexanes (Scheme 3). To the best of our knowledge, Watson and

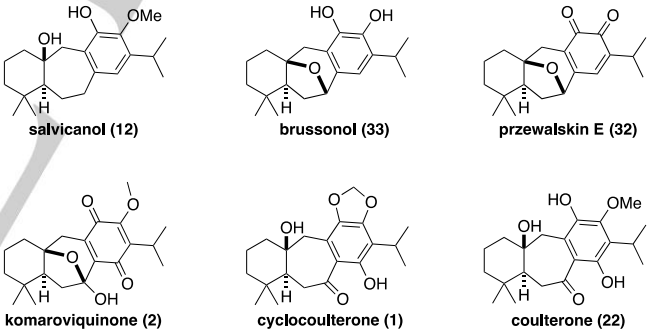
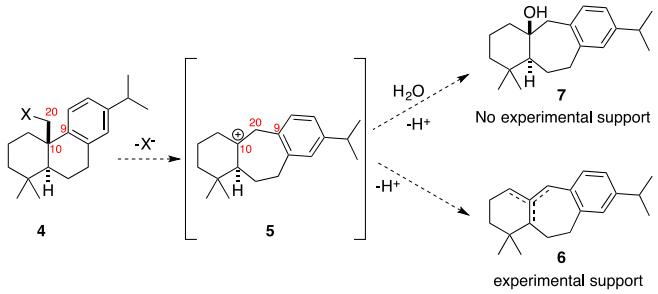


Figure 2. Examples of icetexane subclasses according to Sarpong. [11]**Error! Bookmark not defined.**

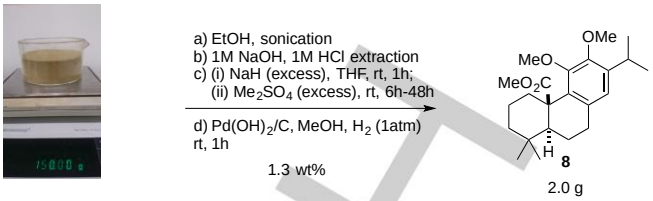
Dominguez were the first to propose such a connection between abietanes and icetexanes,[12] but several other research laboratories have proposed similar mechanisms to connect abietanes to their rearranged congeners. [13] Hydride abstraction from the angular methyl group (X = H) or solvolysis of the primary alcohol (X = OH) of abietane **4** generates a primary cation that could immediately rearrange to the more stable ring expanded tertiary carbocation **5** forming the icetexane core structure. Ring expansions which lead to alkenes **6** *via* a deprotonation of carbocation **5** were experimentally supported. [14] Indeed, such rearrangements were performed by treating primary hydroxyl abietanes such as **4** with either thionyl chloride in dry benzene or *p*-TsCl in dry pyridine to yield alkene icetexanes such as **6**. [14] Although trapping of carbocation **5** by a water molecule was frequently suggested to access icetexanes

bearing a C10 hydroxyl group such as in alcohol **7**, no experimental evidence of such a mechanism was reported. [13] In this study, we provide the first experimental evidence which is supporting this transformation. In particular, we demonstrate that no enzymes are necessary for the attack on the β-face.



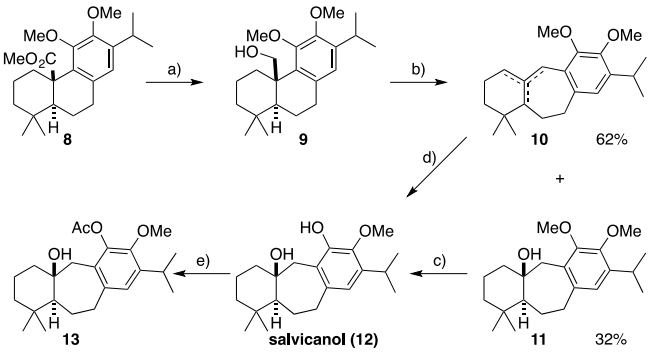
Scheme 3. Hypothetical biogenetic abietane ring expansion to icetexanes. X = H or OH.

The synthesis started with carnosic acid, a commercially available and naturally abundant abietane. [15] Carnosic acid is found in significant amount in *Lamiaceae* and particularly in *Rosmarinus officinalis* and *Salvia officinalis*. The content of carnosic acid in the dried leaves is varying in proportion from 1% to 10% (by weight), depending on the species, the plant age and the environmental stress. [16] The extraction, purification and isolation of carnosic acid was achieved by HPLC from crushed and dried leaves of rosemary (*Rosmarinus officinalis*, origin: Portugal) as reported by Albu et al. [17] However, the triple methylation of pure carnosic acid using the modified conditions of Theoduloz *et al.* resulted only in a moderate yield of **8** (66%).[18] Encouraged by literature reports of related constituents of rosemary, we changed our strategy in order to obtain higher quantities of ester **8**. [17], [19] In this regard, the dried ethanolic extract of rosemary was dissolved in Et_2O and extracted with NaOH (1 M) in order to form the aqueous soluble sodium salts of different phenols. Acidification (1 M aq. HCl) and ethereal extraction of the aqueous phase yielded an phenolic abietane enriched extract, which was subjected to the exhaustive methylation (NaH, Me_2SO_4, THF, then MeOH) to yield a mixture of the desired trimethylated carnosic acid **8** and by-products. The mixture was further refined by dissolving the constituents in MeOH, filtration, and subsequent hydrogenation using $Pd(OH)_2$ /C resulted in pure dimethoxy canosiate methyl ester **8** (1.3 weight% from dried and crushed rosemary). A smooth reduction of the angular methoxy ester group of **8** was achieved *via* a modified literature protocol using LAH in hot ether, which resulted in alcohol **9** in excellent yield (89%, Scheme 5). [20]



Scheme 4. Isolation and derivatization of carnosic acid.

Having the desired alcohol **9** in hand, we wanted to experimentally investigate the ring expansion hypothesis as outlined above in Scheme 3. To this end, the primary alcohol **9** was treated with different acids in aqueous solution. Only strong acids were able to promote a ring expansion leading to an inseparable mixture of alkenes **10** in low yields. Furthermore, such harsh conditions prevented the formation of alcohol **11**, probably due to direct elimination. Finally, basic treatment of **9** (MsCl, Et_3N in THF followed by addition of water) resulted in the tertiary alcohol **11** bearing the icetexane skeleton in 32% yield as a mixture with isomeric olefins **10** in an excellent overall yield of 94%. This remarkable transformation warrants a number of mechanistic comments. First, it is likely that the mesylate undergoes E_1 elimination to generate the primary cation. As can be deduced from the product, a cation similar to **5** would have to be generated *via* an 1,2-alkyl shift. Alternatively, a concerted process merging these two steps could be operative. The next step now constitutes the key scientific problem, which has been debated in the literature for decades. [12], [13] The attack of water on such a carbocation was suggested to be disfavored from the β-face according to Dreiding models and therefore supporting an enzymatically guided attack.[21] However, our exclusively observed β-selectivity refutes this enzymatic hypothesis and thus establishes a non-enzymatic mechanism. [21] This ring expansion presents the first experimental study that invokes a water mediated trapping of a tertiary carbocation such as **5**. This constitutes the first experimental confirmation that validates the biosynthetic hypothesis of icetexane bearing a C10 tertiary alcohol, shown earlier (Scheme 3).



Scheme 5. Preparation of salvicanol (**12**) based on a biogenetic ring expansion hypothesis: a) LAH, Et_2O, 45 °C, 6 h, 89%; b) MsCl, Et_3N, THF, –10 °C, 20 min; H_2O, 40 °C, 12 h, 94%; c) L-Selectride solution in THF, 80 °C, 2 h, 80%; d) (i) *m*-CPBA, CH_2Cl_2, 0 °C, 2 h; (ii) L-Selectride (excess) solution in THF, 80 °C, 3 h, 42% (2 steps); e) Ac_2O, pyridine, rt, 1 h, 90%.

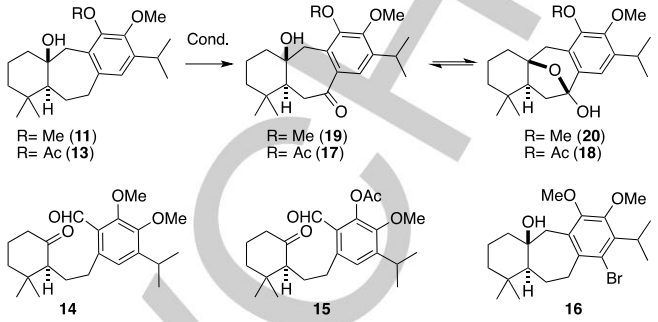
A selective hydride mediated demethylation (L-selectride in THF, 80 °C, 2 h) originally developed by Majetich *et al.* was successfully applied to the tertiary alcohol **11**.[22] Indeed, the sterically less congested C11 methoxy group was selectively demethylated with complete regioselectivity in high yield (80%), leading to the first synthesis of salvicanol (**12**). All spectroscopic data are in agreement with those reported for the natural sample.[23] The alkenes **10**, obtained in the course of the ring expansion of **9**, could be converted to salvicanol (**12**) in two consecutive steps consisting of an epoxidation carried out using *m*-CPBA[24] and a well-established one-pot hydride (L-selectride) mediated epoxide opening/demethylation in 42% yield over two steps.[25] Salvicanol (**12**) could also be acetylated in high yield (90%) to afford salvicanol acetate (**13**), which was used later on for the subsequent oxidation.[23]

Experimental evidence for abiotic benzo[1,3]dioxole formation.

Having the methyl and acetyl derivatives of salvicanol (**11** and **13**, respectively), a C7 benzylic oxidation as well as an aromatic oxidation constituted the missing steps to accomplish the synthesis of komaroviquinone (**2**). Majetich and co-workers reported a difficult C7 benzylic oxidation of a substrate, which is very similar to **12** and **13**.[26] They concluded that the C10 OH-group would not tolerate oxidative conditions and result in a C10-C20 oxidative cleavage. These results could be reproduced with substrate **12** and **13** using similar conditions (CrO_3, AcOH/H_2O, Table 1, entry 1 and 2), giving rise to the unstable aldehydes **14** and **15**, but only trace amounts were obtained. Further attempts involving the possible formation of benzylic radicals, such as the use of KBr in presence of Oxone® (entry 3) resulted in the formation of the side-product **16**, presumably *via* the bromination with a Br^+ species.[27] The transition metal free oxidation of **13** using TBHP under microwave conditions (180 °C, CH_3CN, entry 4) resulted in trace amounts of the desired ketone **17** (detected by ^{1}H-NMR).

The successful formation of **17** in presence of TBHP encouraged us to investigate different combinations of transition metal catalysts with TBHP (entries 5-12). Indeed, the formation of the desired product **17** was observed by utilizing several transition metals (entries 6-9, and 11-12). The optimal conditions were identified when reacting acetate **13** under a modified Hirao protocol ($RuCl_3$•xH_2O, TBHP, entry 12).[28] The benzylic oxidation product **17** was obtained in moderate yield (31%) along with starting material (**13**, 19%). NMR analysis of this compound was difficult due to the keto-hemiketal tautomerism equilibrium between the open (**17**) and the closed form (**18**), as already observed on a similar hydroxy- ketone by Suto and co-workers.[29] Conditions using transition metals without TBHP were also investigated (entries 13-16).[30] However, compounds **19** (and **20**, entry 16) or **17** (and **18**, entries 13 and 15), were produced only in trace amounts. These experiments led to the identification of $RuCl_3$/TBHP as optimal oxidant, which was used in the synthesis (Scheme 6).

Table 1. Benzylic oxidation of the salvicanol derivatives.



Entry	Conditions	Substrate	Observations
1	CrO_3	**11**	**14**[a]
2	CrO_3	**13**	**15**[a]
3	KBr, Oxone, DCM/H_2O	**11**	**16**[a]
4	TBHP, MW	**13**	**17**[a]
5	$Cr(CO)_6$, TBHP	**11**	No conversion
6	$Cr(CO)_6$, TBHP	**13**	**17**: 10%
7	$Rh_2(cap)_4$, TBHP	**13**	**17**[a]
8	$Ru(Cl)_2(PPh_3)_2$, TBHP	**13**	**17**:10%, **13**: 40%
9	$ReOCl_3(OPPh_3)(SMe)_2$, TBHP	**13**	**17**[a]
10	VCp_2Cl_2, TBHP	**13**	No conversion
11	Bi(0), picolinic acid, TBHP	**13**	**17**: 17%, **13**: 13%
12	$RuCl_3$•xH_2O, TBHP	**13**	**17**: 31%, **13**: 19%
13	$Fe(OTf)_2$, ligands, H_2O_2	**13**	**17**[a]
14	$NaIO_4$, $RuCl_3$•xH_2O	**13**	Complex mixture
15	$KMnO_4/CuSO_4$•5H_2O	**13**	**17**[a]
16	$KMnO_4/CuSO_4$•$_5$$H_2O$	**11**	**19**[a]

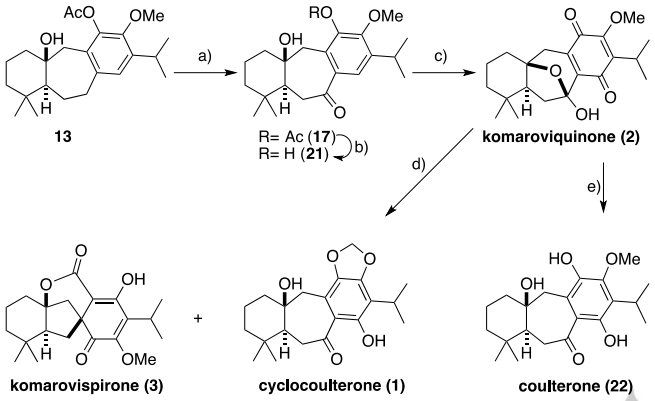
[a] Observed in trace amounts.

For the completion of the synthesis of komaroviquinone (**2**, Scheme 6), the ketone **17** was first deacetylated using KOH in methanol at rt for 12 h. The crude mixture was subsequently submitted to aromatic oxidation to phenol **21** using salcomine in an O_2 atmosphere with strict exclusion from light to yield synthetic komaroviquinone (**2**) in 56% yield over two steps. This modest yield could be explained by the C7 keto group, which lowers the electron density of the aromatic ring and therefore decreases the reactivity towards oxidation. Furthermore, komaroviquinone (**2**) was obtained as the sole tautomer, which could be explained by the newly formed H-bond at the C14-keto group, and by the increased electrophilicity of the C7 vinylogous ketone compared to the benzylic ketone in structure **17**.

Next, the photolysis of komaroviquinone (**2**), applying similar conditions as used for the synthesis of taiwaniaquinol A (Et_2O, sunlight, rt), was carried out.[8] We were delighted to observe the formation of the cyclocoulterone (**1**) as well as the known komarovispirone (**3**) in nearly equimolar ratio with an overall

yield of 63%. These findings further supported our previously non-enzymatic biogenetic hypothesis for the biosynthesis of such methylenedioxy bridge natural product. In addition, this experiment also yielded for the first time synthetic cyclocoulterone (**1**).

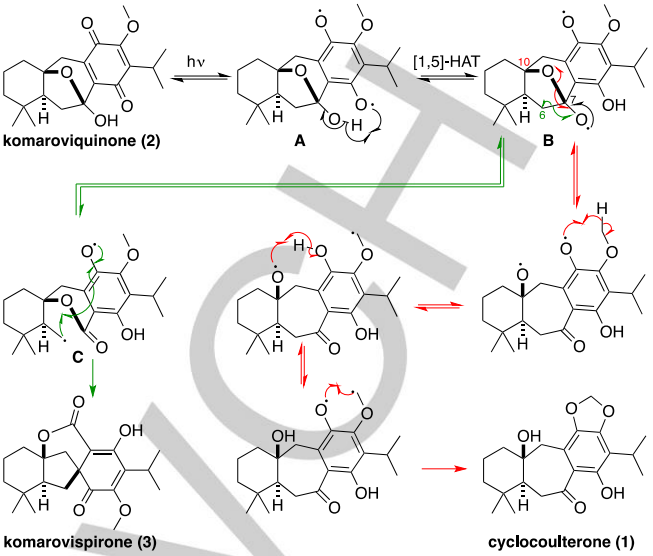
Additionally, komaroviquinone **2** was reduced in an ethereal solution using an aqueous solution $Na_2S_2O_4$ in a separatory funnel at rt for 1 min, which afforded coulterone (**22**) in high yield (82%). This natural product was isolated over 20 years ago, [31] but has so far never been synthesized.



Scheme 6. Completion of the synthesis of komaroviquinone (2): a) $RuCl_3 \cdot xH_2O$, CH_2Cl_2/Pyr, *t*-BuOOH, 50 °C, 12 h, 31%, 50% brsm; b) KOH, MeOH, rt, 12 h; c) Salcomine, O_2 (5 bar), MeCN, 12 h, 56% (2 steps); d) Sunlight, Et_2O, 4°C (winter), 45 min, 63%; e) $Na_2S_2O_4$ (aq.), Et_2O, 1 min.

The previous photolysis of komaroviquinone (**2**), achieved with a low-pressure mercury lamp by Majetich and co-workers in cyclohexane, lead to the formation of komarovispirone (**3**) as the sole product.[10] However, under sunlight irradiation, the formation of an additional unknown compound in a $CDCl_3$ solution was reported. This by-product could correspond to cyclocoulterone (**1**), but no analytical data was reported[10] to verify this hypothesis.

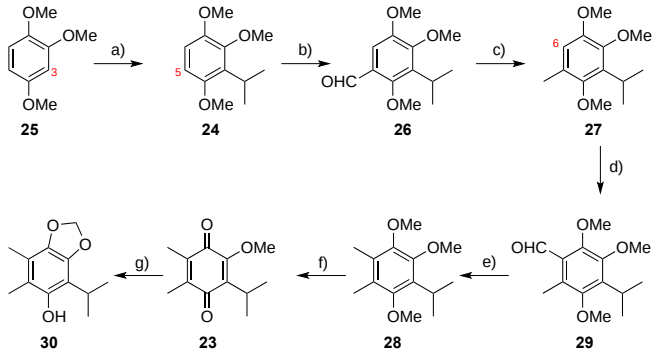
A possible mechanism to rationalize the formation of cyclocoulterone (**1**), in accordance with the suggested proposal for the formation of komarovispirone, [10] is depicted in Scheme 7. Light excitation of the n → π^* transition of the quinone **2** could generate the quinol diradical **A** that could undergo a 1,5 H-atom transfer (HAT) between the alkoxy radical at C14 and the hydroxyl group at C7 to give **B**. At this point, the compound **B** could either fragment at the C6-C7 bond to form the biradical **C**, which recombined to komarovispirone (**3**), or at the C7 O(C10) ether bond, which after successive 1,5 and 1,6 HAT respectively, recombine to yield cyclocoulterone (**1**).



Scheme 7. Proposed mechanism for the co-formation of cyclocoulterone (1) and komarovispirone (3) through the photolysis of komaroviquinone (2).

Model substrate synthesis and photolysis.

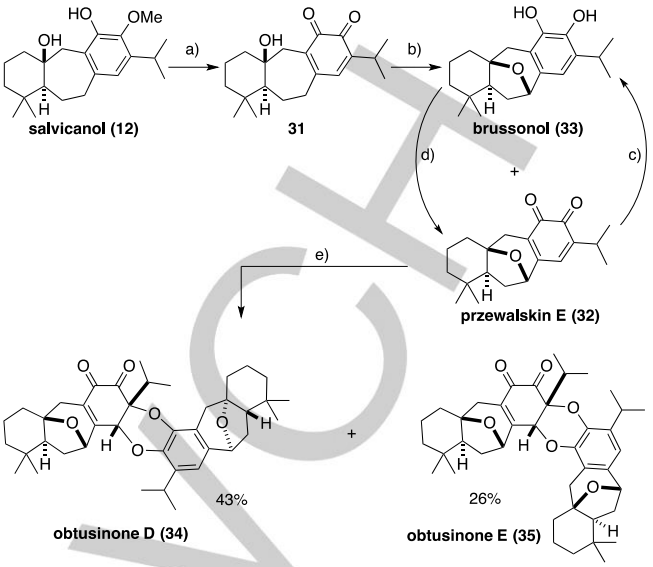
The generality of this reaction was investigated by using a non-natural model substrate. The synthesis of fully substituted quinone **23** (Scheme 8) was therefore engaged starting with the 1,2,4-trimethoxy-3-isopropyl benzene (**24**), which was obtained *via* known procedures from the commercially available **25** in two steps in 45% overall yield. [32] Rieche formylation of **24** yielded aldehyde **26** in an excellent yield of 96%. The C=O group of **26** was reduced using $Pd(OH)_2$/C in methanol under H_2 pressure (80 bar) and the electron rich methylphenyl **27** was obtained in good yield (77%). The same formylation and reduction sequence then furnished the hexasubstituted benzene **28**, *via* aldehyde **29**, in a good overall yield of 84%. Silver(II) oxide demethylative oxidation of catechol **28** succeeded to provide the quinone **23** in good yield (62%). Having this model system in hand, the remote C−H functionalization was explored with quinone **23**. Applying the conditions developed earlier (direct sunlight, Et_2O, rt) led to a full conversion of the starting material (observed by decoloration of the reaction mixture and confirmed by TLC analysis), however, without formation of the desired methylenedioxy bridge. Different solvents (benzene, *t*-BuOH, $CHCl_3$) and light sources (sunlight, medium pressure mercury lamp) were evaluated next. Photolysis of **23** in *t*-BuOH was effective and resulted in the formation of the desired compound featuring the methylenedioxy bridge **30** in 47% yield using a medium pressure Hg lamp at room temperature. The feasibility of this reaction in *t*-BuOH rather than in Et_2O could be explained by the higher ability of *t*-BuOH to form hydrogen bonds with a phenolxyl radical and stabilizea putative biradical species, which would favor the formation of the methylenedioxy bridge **30**.



Scheme 8. Synthesis of model substrate 23 and its photolysis: a) Ref.[32], 45% over 2 steps; b) $TiCl_4$, CH_2Cl_2, Cl_2CHOMe, −10 °C to rt, 2 h, 96%; c) $Pd(OH)_2/C$, MeOH, H_2 (80 bar), 24 h, 77%; d) $TiCl_4$, CH_2Cl_2, Cl2CHOMe, −10 °C to rt, 12 h, 98%; e) $Pd(OH)_2/C$, MeOH, H_2 (80 bar), 18 h, 86%; f) AgO, HNO_3, (6 M), dioxane, rt, 80 min, 62%; g) Medium pressure Hg-lamp, t-BuOH, 45 min, rt, 47%.

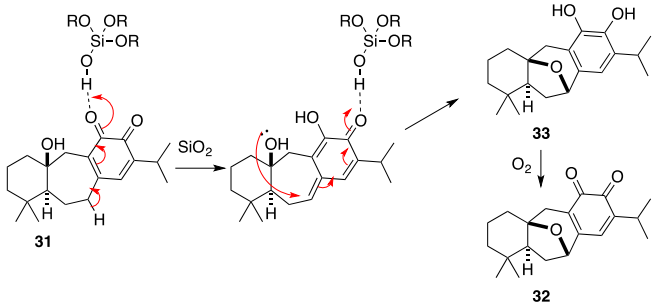
Synthesis of members of the barbatusol class.

Having salvicanol (**12**) in hand, syntheses of several barbatusol natural products[11] were investigated (Scheme 9). A demethylative oxidation of salvicanol (**12**) using DDQ in aqueous acetone generated the orthoquinone **31** in excellent yield (96%), after aqueous workup. [24], [33] However, purification by silica was difficult, as **31** was reacting further. Therefore, we investigated the outcome of a prolonged exposure of orthoquinone **31** on silica gel upon adsorption. The quinone **31** was dissolved in ether, adsorbed on silica, with subsequent removal of the solvent. After 48 h at rt, this impregnated silica was subsequently purified by flash chromatography on silica gel to afford two main products, identified as przewalskin E (**32**) and brussonol (**33**). Interestingly, when the adsorbed orthoquinone (**31**) was left in an open flask with frequent mixing of the impregnated silica powder (every 4 hours), a higher yield of oxidized przewalskin E (**32**, 50%) was obtained without detectable formation of brussonol (**33**).



Scheme 9. Synthesis of przewalskin E (**32**), brussonol (**33**) and first synthesis of obtusinones D (**34**) and E (**35**): a) DDQ, aq. acetone, rt, 10 min., 96%; b) SiO_2, 48 h, 39–50% (2 steps); c) $Na_2S_2O_4$ (aq.), Et_2O, 1 min, 94%; d) DDQ, dioxane, 80% e) Neat, 100 °C, 6 h, 69%.

The outcome of this reaction could be rationalized by a silica gel acid catalyzed tautomerization (Scheme 10), forming a reactive quinone-methide intermediate, which upon nucleophilic attack of the angular C10-OH group could result in brussonol (**33**). Upon aerobic conditions, **33** can be further converted into its natural congener przewalskin E (**32**). Majetich and co-workers already reported such a synthesis of brussonol (**33**) from **31** through heating a concentrated solution of **31** in Et_2O (60 °C, 40 h, 70%).[24] Similarly, Takeya and co-workers described the same transformation by heating **31**, adsorbed on magnesium silicates (Florisil®) in a microwave oven (150 °C, 5 min, 37%).[33b] However, none of these methods were suitable to produce przewalskin E (**32**) directly from **31**. Interestingly, only very few reports of catechol oxidation to orthoquinone mediated on silica gel under aerobic conditions are described. Futhermore, the crucial role of silica gel was further substantiated by experiments, when an acetonitrile or acetone solution of brussonol was stirred under oxygen atmosphere, and only trace amounts of przewalskin E (**32**) could be obtained after several days.



Scheme 10. Mechanistic proposal for the formation brussunol (**33**) und przewalskin E (**32**).

Synthesis of the proposed structure 32 of przewalskin E and a proposal for revision of its constitution.

Formation of such a reactive quinone methide from orthoquinone **31** and aerobic catechol oxidation under comparable reaction conditions were already reported by Burnell and co-workers. [35] Brussonol (**33**) was first isolated from *Salvia brussonetii* and shows insecticidal and anti-P388 leukemia cell acitivity. The spectral data of **33** were in good agreement with those reported for the natural and synthetic products. [13]c, [33]b The spectral data quinone **32**, first synthetically prepared from natural demethylsalvicanol, [33]b and subsequently isolated from *Salvia przewalskii MAXIM,* [36] corresponds perfectly to the synthetic material, but significantly deviates from the natural sample. Although the ^{13}C-NMR chemical shifts (0.1-0.4 ppm) and the optical activity of the isolated sample reasonably matches with our synthetic substance, the ^{1}H-NMR chemical shifts (0.01-0.08 ppm) and FT-IR absorption bands (the main signal at 1660 cm^{-1} was not reported, and signals at 1722, and 1680 cm^{-1} were found with much lower intensity) significantly diverges from the synthetic samples. Moreover, the natural compound was isolated as a white powder and our synthetic sample as a red amorphous solid, the typical color of orthoquinones. Unfortunately, the authors did not compare their sample with the synthetic compound of Takeya. [33b] However, the structure of **32** could be verified by interconverting it to brussonol (**33**) by reduction with aqueous $Na_2S_2O_4$ in excellent yield (94%). The resulting **33** was then oxidized back to **32** following the Takeya protocol (DDQ, dioxane).[33]b As the preparation of the proposed structure of **32** resulted in non-identity to the natural product as judged by different data, we propose that a structural reassignment of przewalskin E is necessary.

Synthesis of the proposed structure dimeric C_{40} terpenes obtusinone D and E. Reassignment of the configuration of obtusinone D.

Having strong experimental evidence for the structure of synthetic **32** (via reduction to known brussonol (**33**) and subsequent re-oxidation), the synthesis of the unusual dimeric icetexanes obtusinones D (**34**) and E (**35**) was addressed next (Scheme 9). The first reported example of such an icetexane dimer was grandione, which was isolated by Riccio *et al.* in 1999 from *Toreya grandis*[37] and synthesized by Takeya and co-workers in 2005 (and the structure was reassigned) [38] *via* a solid state hetero-Diels-Alder dimerization of orthoquinone **31**. Obtusinone D (**34**) and E (**35**), which were recently isolated by Salae and Boonnak, were suggested to biogenetically originate from a similar Diels-Alder dimerization of przewalskin E (**32**). [39] Having **32** in hand, modified Takeya conditions (neat, 100 °C, 6 h) were applied to achieve the first synthesis of both obtusinone D (**34**) and E (**35**) (1.7 : 1.0), in high overall yield (69%). The separation of both synthesized natural products proved to be difficult, using either flash chromatography or preparative TLC on silica gel utilizing the eluent reported in the isolation study. [39] We expected that the π-stacking of both natural products could be responsible for the identical retention time. Consequently, we decided to change our eluent system by adding toluene to our solvent mixture in order to break the π-stacking interaction between **34** and **35**. Gratifyingly, the synthetic compounds were then successfully separated by preparative TLC with an optimized eluent (pentane/toluene/Et_2O, 5/5/1). The spectral data of both synthetic natural products was in perfect agreement with the natural samples. However, an X-ray analysis of a single crystal of obtusinone D (**34**, Figure 3) could be obtained and the structure shows an opposite C13 and C14 configuration as reported by Salae and Boonnak.[39] Indeed, their study established the C13 and C14 configurational assignment of **34** based on a NOESY correlation between H7 and H14 and between H14 and Me16. The close proximity of H7 and H14 revealed by the X-ray crystallographic analysis of **34** (Figure 3), could explain the NOESY correlation measured by Salae and Boonnak[39] between these two centers. This NOESY correlation was later observed by us, therefore further substantiating the identity of our synthetic obtusinone D to the natural product.

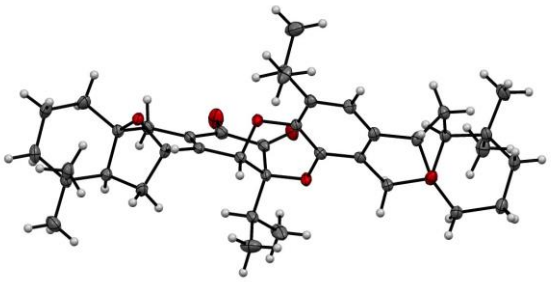


Figure 3. X-ray crystallographic analysis of **34**. Red = oxygen, grey = carbon, white = hydrogen.

The X-ray crystallographic analysis of synthetic obtusinone D in combination with the matching spectral data for both natural and synthetic samples therefore unambiguously requires the structural reassignment of the natural product, which should as a consequence be represented by the revised structure **36** (Figure 4, B). Consequently, the C13 and C14 configuration of obtusinone E is suggested to be identical with the one of obtusinone D, as shown for the revised structure **37** (Figure 4, B).

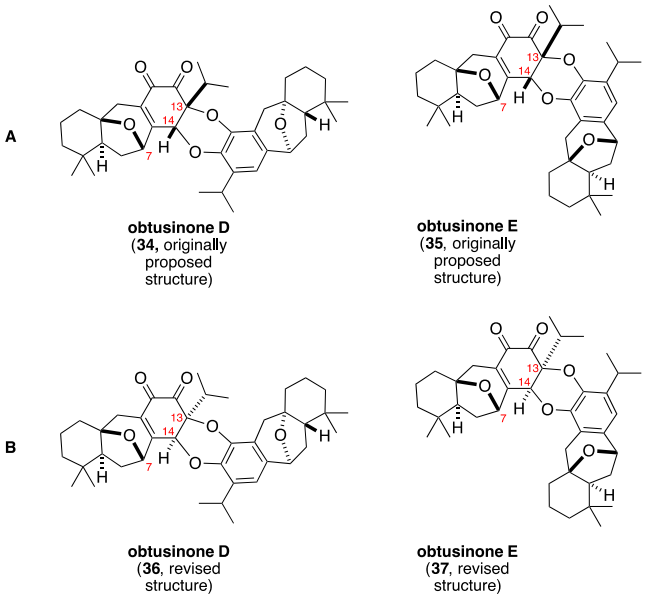


Figure 4. A) Originally proposed and B) revised structure of obtusinones D and E.

The different ratio detected for the isolated natural products (**36**:**37**, 4:1) compared to the one obtained by synthesis (**36**:**37**, 1.7:1.0) could be explained by the higher temperature needed to achieve the Diels-Alder reaction in high yield and reasonable reaction time in the chemical laboratory.

Conclusions

A divergent, elegant and short synthesis of ten members of the icetexane family of natural products was achieved in four to nine steps from abundant (+)-carnosic acid, isolated from *Rosmarinus officinalis*. Among these members, (+)-salvicanol (**12**), (−)-cyclocoulterone (**1**), (−)-coulterone (**22**), (−)-obtusinone D (**36**) and (−)-obtusinone E (**37**) were synthesized for the first time. A straightforward, inexpensive and efficient sequence, consisting of methylation and hydrogenation of rosemary ethanol extracts enriched with carnosic acid and related congeners was developed to obtain the desired trimethyl carnosic acid **8** in high yield. Salient features of the synthesis of salvicanol (**12**) include a single step biomimetic ring expansion of the abietane **9** to the icetexane **11**, bearing an angular hydroxyl group at C10. This constitutes the first experimental evidence for a tertiary carbocation trapping such as **5** by a water molecule, and a selective aromatic demethylation. (+)-Salvicanol (**12**) was used as a common intermediate to synthesize: (A) (−)-brussonol (**33**) and the reported structure pf (−)-przewalskin E (**32**) in two steps *via* an aromatic oxidation to form the orthoquinone **31**, followed by an aerobic silica gel based tautomerization and oxidation; (B) (−)-obtusinone D (**36**), which was structurally reassigned, and (−)-obtusinone E (**37**), through a hetero-Diels-Alder of (−)-przewalskin E (**32**); (C) (+)-komaroviquinone (**2**) *via* a selective benzylic oxidation and an aromatic oxidation; (D) (−)-cyclocoulterone (**1**) and (+)-komarovispirone (**3**) by a sunlight photolysis of (+)-komaroviquinone (**2**). This result supports our previous biogenetic hypothesis for the non-enzymatic formation of methylenedioxy catechol natural products; and finally, (E) (−)-coulterone (**22**) through hydrogenation of (+)-komaroviquinone (**2**).

Experimental Section

For the details of all experiments, see the Supporting Information.

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Keywords: remote C-H activation • cyclocoulterone • icetexane • ring expansion • hetero Diels-Alder

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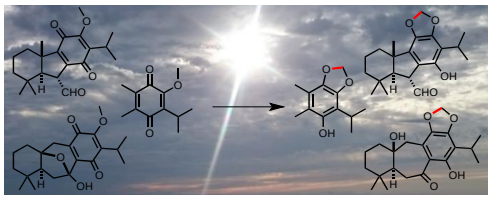

Let the sun shine in! A collective synthesis of ten members of icetexanes natural products was completed based on several biogenetic hypotheses. Among these members (–)-cyclocoulterone was synthesized from (+)-komariviquinone *via* a redox-neutral C–H activation triggered by sunlight.

*Christophe Thommen, Markus Neuburger, and Karl Gademann**

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Collective Syntheses of Icetexane Natural Products Based on Biogenetic Hypotheses