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Natural Products

Collective Syntheses of Icetexane Natural Products Based on Biogenetic Hypotheses

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Abstract: A divergent synthesis of 10 icetexane natural products based on a proposed biogenetic cationic ring expansion of a reduced carnosic acid derivative is described. Of these icetexanes, (+)-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 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 (+)-komarovispirone.

Introduction

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

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 by 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 1) redox-neutral, 2) light-mediated, and, most importantly, 3) without the involvement of any enzymes (Scheme 1, bottom).[8]

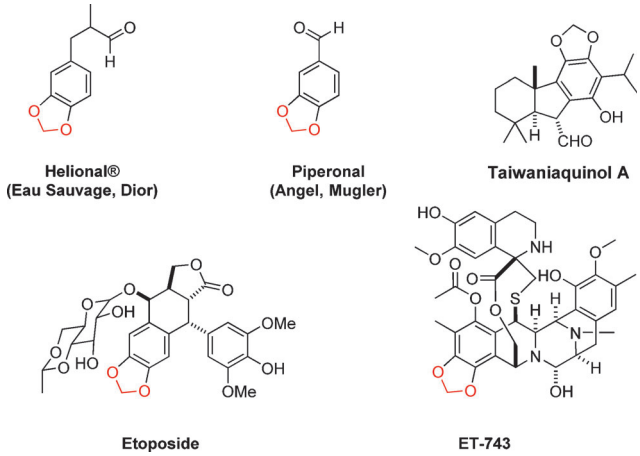
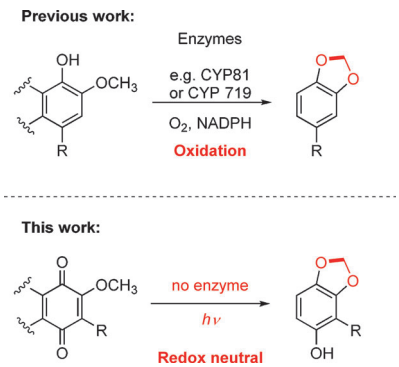


Figure 1. Terpenoids featuring the benzo[1,3]dioxole unit, including those with commercial interest.



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

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In this report we present evidence further corroborating this abiotic hypothesis through the preparation of two benzo[1,3]-dioxole natural products in the chemical laboratory and describe a model study aimed at elucidating the mechanistic details of their synthesis. In addition, we investigated potential routes for the biogenesis of icetexane terpenes and provide 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, the abiotic formation of the complex C_{40} dimers obtusinones D and E is reported and their configurations are reassigned. In summary, the first preparation in synthetic form of five natural products is reported, that is, (+)-salvicanol, (−)-cyclocoulterone, (−)-coulterone, (−)-obtusinone D, and (−)-obtusinone E, along with alternative approaches for the preparation of komaroviquinone, komarovispirone, brussonol, przewalskin E, and demethylsalvicanol quinone.

We have previously reported the photolysis of taiwaniaquinone F to taiwaniaquinol A (Scheme 2A).[8] We hypothesized that such a 1,2,4-hydroxylated aryl moiety incorporating a methylenedioxy bridge can be biosynthetically generated through 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] for producing the methylenedioxy bridge, especially in the plant kingdom in which the use of light as a source of energy is omnipresent. Therefore, the first goal of this study consisted of 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] by an abiotic ring-forming reaction such as that postulated above. In support of the hypothesized biogenetic basis of this transformation, both cyclocoulterone (**1**) and komaroviquinone (**2**) were isolated from the same plant (*Dracocephalum komarovi*), thereby corroborating a possible biogenetic connection between the two natural products.[9] Majetich and Jianhua previously described 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 switch 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**) into cyclocoulterone (**1**) would further substantiate the hypothesized abiotic formation of benzo[1,3]dioxoles. To test this hypothesis, the icetexane precursor **2** first had to be prepared in synthetic form.

Results and Discussion

Investigation of the ring expansion in icetexane biogenesis

Icetexanes are 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 that an abietane precursor such as **4** could be involved in the biosynthetic origin of icetexanes (Scheme 3). To the best of our knowledge, Watson and Dominguez and co-workers 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 can immedi-

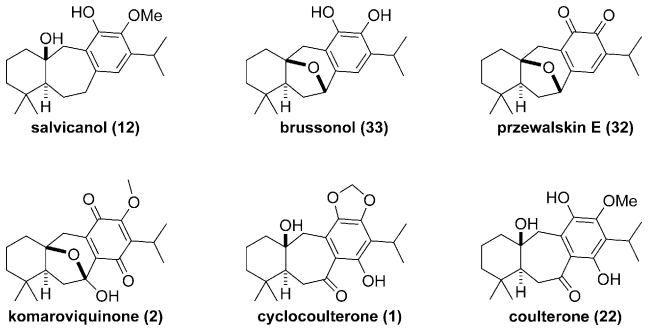
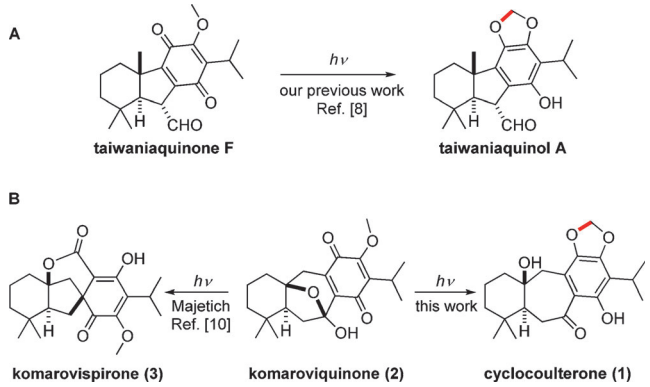
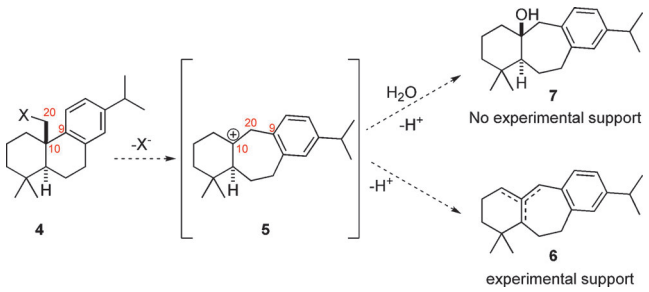


Figure 2. Examples of icetexane natural products.[11]



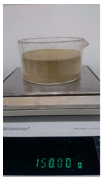
Scheme 2. Remote C–H functionalization of taiwaniaquinone F and komaroviquinone (**2**).



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

ately rearrange to the more stable ring-expanded tertiary carbocation **5** thereby forming the icetexane core structure. Ring expansions leading to alkenes **6** by a deprotonation of carbocation **5** are experimentally supported.[14] Indeed, such rearrangements were performed by treating primary hydroxyabietanes 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 has frequently been suggested as a route to access icetexanes bearing a 10-hydroxy group, such as in alcohol **7**, no experimental evidence of such a mechanism has been reported.[13] In this report, we provide the first experimental evidence in support of this transformation. In particular, we demonstrate that no enzymes are necessary for the attack on the β face.

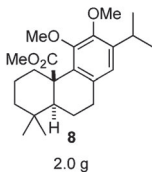
The synthesis started with carnosic acid, a commercially available and naturally abundant abietane.[15] Carnosic acid is found in significant amount in *Lamiaceae* and particularly in *Rosmarinus officinalis* and *Salvia officinalis*. The content of carnosic acid in the dried leaves varies in proportion 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 of 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 by 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 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) to form the aqueous soluble sodium salts of different phenols (Scheme 4). Acidification (1 M aq. HCl) and ethereal



a) EtOH, sonication
b) 1M NaOH, 1M HCl extraction
c) (i) NaH (excess), THF, RT, 1h;
(ii) Me_2SO_4 (excess), RT, 6-48 h

d) $Pd(OH)_2$/C, MeOH, H_2 (1atm)
RT, 1 h

1.3 wt%

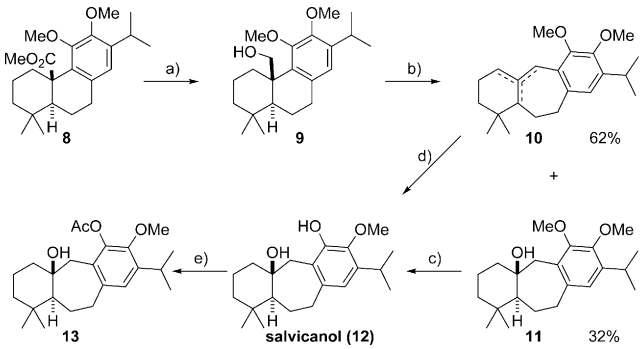


2.0 g

Scheme 4. Isolation and derivatization of carnosic acid.

extraction of the aqueous phase yielded a phenolic abietane-enriched extract, which was subjected to exhaustive methylation (NaH, Me_2SO_4, THF, then MeOH) to yield a mixture of the desired trimethylated carnosic acid **8** and byproducts. The mixture was further refined by dissolving the constituents in MeOH followed by filtration and subsequent hydrogenation using $Pd(OH)_2$/C, which resulted in pure dimethoxycarnosate methyl ester **8** (1.3 wt% from dried and crushed rosemary). A smooth reduction of the angular methoxy ester group of **8** was achieved by a modified literature protocol using lithium aluminium hydride (LAH) in hot diethyl ether, which resulted in alcohol **9** in excellent yield (89%, Scheme 5).[14b]

Having the desired alcohol **9** in hand, we wished to experimentally investigate the ring-expansion hypothesis as outlined



Scheme 5. Preparation of salvicanol (**12**) based on a biogenetic ring-expansion hypothesis. Reagents and conditions: 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%.

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 the addition of water) resulted in the tertiary alcohol **11** bearing the icetexane skeleton in a yield of 32% 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 through a 1,2-alkyl shift. Alternatively, a concerted process in which these two steps merge could be operative. The next step now constitutes the key scientific problem and 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, therefore supporting an enzymatically guided attack.[13b] However, our exclusively observed β selectivity refutes this enzymatic hypothesis and thus establishes a non-enzymatic mechanism.[13b] This ring expansion is the first experimental study invoking a water-mediated trapping of a tertiary carbocation such as **5**. In addition, this is the first experimental validation of the hypothesized biosynthetic formation of icetexane bearing a C10 tertiary alcohol, shown earlier (Scheme 3).

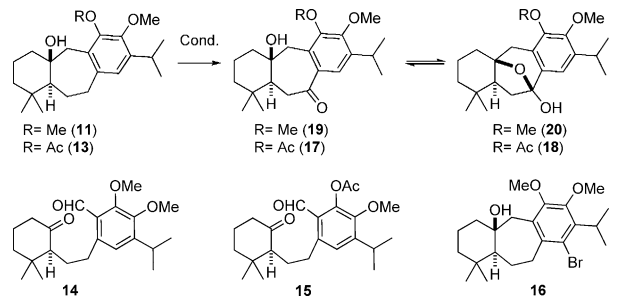
A selective hydride-mediated demethylation (L-selectride in THF, 80 °C, 2 h) originally developed by Majetich et al. was successfully applied to the tertiary alcohol **11**.[20] Indeed, the sterically less congested 11-methoxy group was selectively demethylated with complete regioselectivity in high yield (80%) to result in the first synthesis of salvicanol (**12**). All the spectroscopic data gave good agreement with those reported for the natural sample.[21] The alkenes **10**, obtained in the course of the ring expansion of **9**, were converted into salvicanol (**12**) in two consecutive steps consisting of an epoxidation carried out by using *m*-chloroperoxybenzoic acid (*m*-CPBA)[22] and a well-

established one-pot hydride (L-selectride)-mediated epoxide opening/demethylation in a yield of 42% over the two steps.[23] Salvicanol (**12**) was acetylated in high yield (90%) to afford salvicanol acetate (**13**), which was used later on for the subsequent oxidation reaction.[21]

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

Having the methyl and acetyl derivatives of salvicanol (**11** and **13**, respectively) in hand, a C7 benzylic oxidation and an aromatic oxidation were required to accomplish the synthesis of komaroviquinone (**2**). Majetich et al. reported a difficult C7 benzylic oxidation of a substrate very similar to **12** and **13**.[24] They concluded that the 10-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** under similar conditions (CrO_3, AcOH/H_2O, Table 1, entries 1 and 2) to give 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 the presence of Oxone® (entry 3), resulted in the formation of the side-product **16**, presumably by bromination with a Br^+ species.[25] The transition-metal-free oxidation of **13** using *tert*-butyl hydroperoxide (TBHP) under microwave conditions (180 °C, CH_3CN, entry 4) resulted in trace amounts of the desired ketone **17** (detected by ^1H NMR spectroscopy).

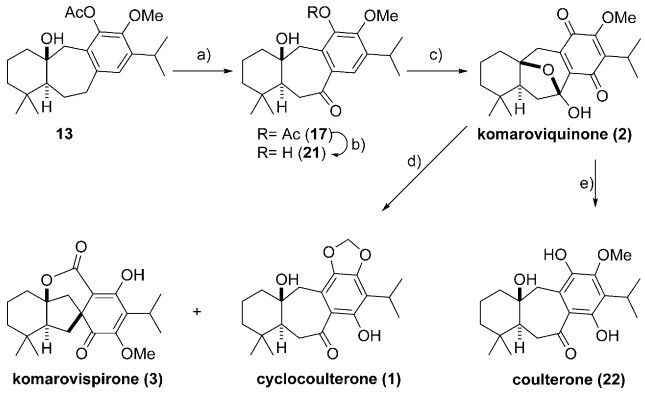
Table 1. Benzylic oxidation of the salvicanol derivatives **11** and **13**.



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, microwave	**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	$RuCl_3{\cdot}xH_2O$, TBHP	**13**	**17**: 31%, **13**: 19%
13	$Fe(OTf)_2$, ligands, H_2O_2	**13**	**17**[a]
14	$NaIO_4$, $RuCl_3{\cdot}xH_2O$	**13**	complex mixture
15	$KMnO_4/CuSO_4{\cdot}5H_2O$	**13**	**17**[a]
16	$KMnO_4/CuSO_4{\cdot}5H_2O$	**11**	**19**[a]

[a] Observed in trace amounts.

The successful formation of **17** in the presence of TBHP encouraged us to investigate different combinations of transition-metal catalysts and TBHP (entries 5–12). Indeed, the formation of the desired product **17** was observed by utilizing several transition metals (entries 6–9, 11, and 12). The optimal conditions were identified when treating acetate **13** under a modified Hirao protocol ($RuCl_3{\cdot}xH_2O$, TBHP, entry 12).[26] The benzylic oxidation product **17** was obtained in moderate yield (31%) along with the starting material (**13**, 19%). NMR analysis of this compound was difficult due to keto–hemiketal tautomerism between the open (**17**) and closed form (**18**), as already observed for a similar hydroxy-ketone by Suto et al.[27] Reaction conditions involving transition metals without TBHP were also investigated (entries 13–16).[28] However, compound **19** (and **20**, entry 16) or **17** (and **18**, entries 13 and 15) was produced only in trace amounts. These experiments revealed $RuCl_3$/TBHP to be the optimal oxidant, and was used in the synthesis (Scheme 6).



Scheme 6. Completion of the synthesis of komaroviquinone (**2**). Reagents and conditions: 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.

To complete the synthesis of komaroviquinone (**2**, Scheme 6), the ketone **17** was first deacetylated by using KOH in methanol at room temperature for 12 h. The crude mixture containing phenol **21** was subsequently submitted to aromatic oxidation using salcomine in an O_2 atmosphere with the strict exclusion of light to produce synthetic komaroviquinone (**2**) in a yield of 56% over two steps. This modest yield could be explained by the presence of 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 presence of the newly formed hydrogen bond at the 14-keto group and by the increased electrophilicity of the C7 vinylogous ketone compared with the benzylic ketone in structure **17**.

Next, komaroviquinone (**2**) was subjected to photolysis, applying similar conditions to those used for the synthesis of taiwaniaquinol A (Et_2O, sunlight, RT).[8] We were delighted to observe the formation of the cyclocoulterone (**1**) as well as the

known komarovispirone (**3**) in a nearly equimolar ratio in an overall yield of 63%. These findings further supported our previously non-enzymatic biogenetic hypothesis for the biosynthesis of such a methylenedioxy-bridged natural product. In addition, this is the first time that synthetic cyclocoulterone (**1**) has been produced.

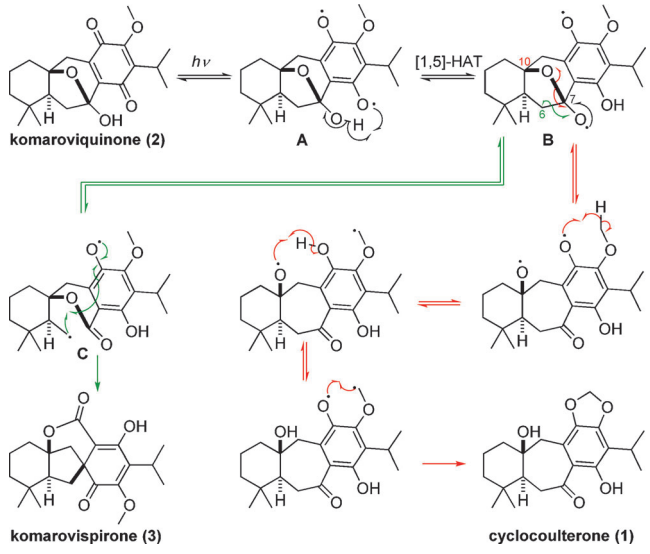
Additionally, komaroviquinone (**2**) was reduced in an aqueous ethereal solution of $Na_2S_2O_4$ in a separatory funnel at room temperature for 1 min to afford coulterone (**22**) in high yield (82%). This natural product was isolated over 20 years ago,[29] but had never been synthesized.

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

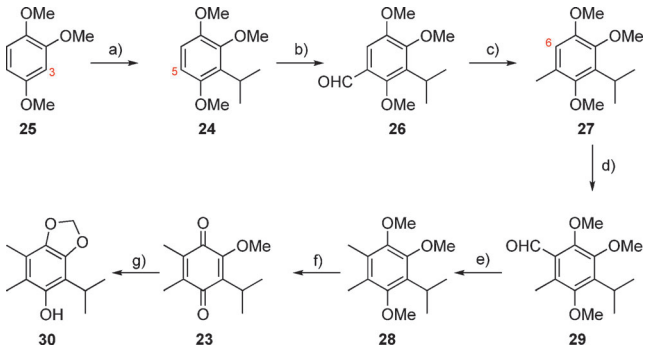
A possible mechanism to rationalize the formation of cyclocoulterone (**1**), in accordance with the suggested proposal for the formation of komarovispirone (**3**),[10] is depicted in Scheme 7. Light excitation of the n→π* transition of the quinone **2** could generate the quinol diradical **A**, which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

Model substrate synthesis and photolysis

The generality of this reaction was investigated by using a non-natural model substrate. The fully substituted quinone **23** (Scheme 8) was therefore synthesized from 1,2,4-trimethoxy-3-isopropylbenzene (**24**), which was obtained from the commercially available **25** in two steps in an overall yield of 45%.[XXX] Rieche formylation of **24** yielded aldehyde **26** in an excellent yield of 96%. The C=O group of **26** was reduced by 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, remote C–H functionalization was explored with quinone **23**. Applying the conditions developed earlier (direct sunlight, Et_2O, RT) led to full conversion of the starting material (observed by the decoloration of the reaction mixture and confirmed by TLC analysis), however, without the formation of the desired methylenedioxy bridge. Different solvents (benzene, *t*BuOH, $CHCl_3$) and light sources (sunlight, medium-pressure mercury lamp) were evaluated next. The photolysis of **23** in *t*BuOH was effective and resulted in the formation of the desired compound **30** featuring the methylenedioxy bridge in a yield of 47% by using a medium-pressure mercury 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 phenoxyl radical and stabilize a putative biradical species, which would favor the formation of the methylenedioxy-bridged compound **30**.



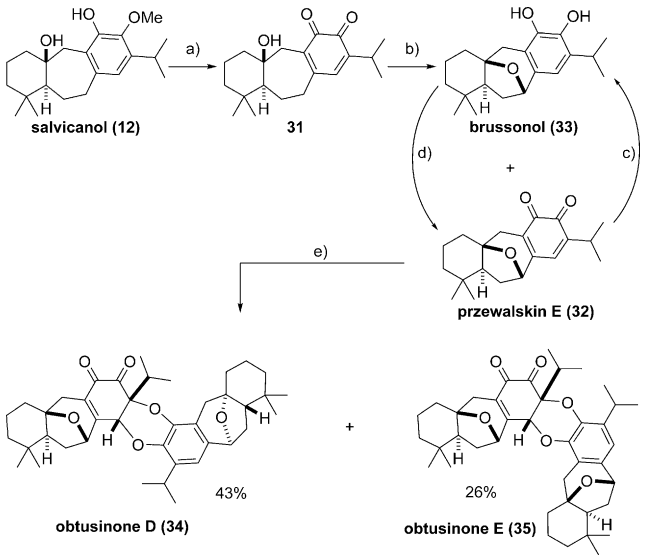
Scheme 7. Proposed mechanism for the co-formation of cyclocoulterone (**1**) and komarovispirone (**3**) through the photolysis of komaroviquinone (**2**).



Scheme 8. Synthesis of model substrate **23** and its photolysis. Reagents and conditions: a) see ref. [XXX], 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, Cl_2CHOMe, −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 natural products

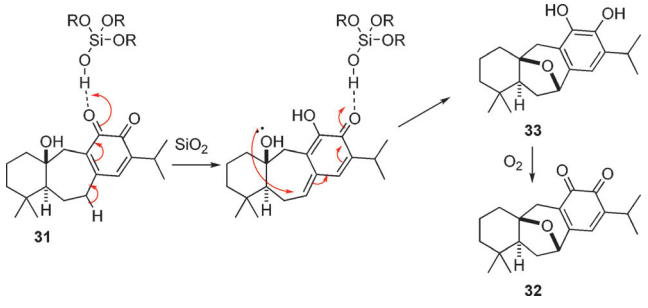
Having salvicanol (**12**) in hand, the synthesis of several barbatusol natural products[11] was investigated (Scheme 9). Demethylative oxidation of salvicanol (**12**) by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in aqueous acetone generated the *o*-quinone **31** in excellent yield (96%) after aqueous workup.[22,30] However, purification by silica was difficult, as **31** reacted further. Therefore, we investigated the outcome of prolonged exposure of *o*-quinone **31** to silica gel upon adsorp-



Scheme 9. Synthesis of przewalskin E (**32**), brussonol (**33**), and first synthesis of obtusinones D (**34**) and E (**35**): Reagents and conditions: a) DDQ, acetone (aq.), 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%.

tion. The quinone **31** was dissolved in diethyl ether, adsorbed on silica, and subsequently the solvent was removed. After 48 h at room temperature, this impregnated silica was purified by flash chromatography on silica gel to afford two main products identified as przewalskin E (**32**) and brussonol (**33**). Interestingly, when the adsorbed *o*-quinone **31** was left in an open flask with frequent mixing of the impregnated silica powder (every 4 h), a higher yield of oxidized przewalskin E (**32**, 50%) was obtained without any detectable formation of brussonol (**33**).

The outcome of this reaction could be rationalized by a silica gel acid-catalyzed tautomerization (Scheme 10), with the formation of a reactive quinone methide intermediate, which, upon nucleophilic attack of the angular 10-OH group, could result in brussonol (**33**). In aerobic conditions, **33** can be further converted into its natural congener przewalskin E (**32**). Majetich and Zou have already reported such a synthesis of brussonol (**33**) from **31** through the heating of a concentrated solution of **31** in Et_2O (60 °C, 40 h, 70%).[22] Similarly, Takeya and co-workers described the same transformation by heating



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

31 adsorbed on magnesium silicates (Florisil®) in a microwave oven (150 °C, 5 min, 37%).[30b] However, none of these methods was suitable for producing przewalskin E (**32**) directly from **31**. Interestingly, very few reports of catechol oxidation to *o*-quinone mediated on silica gel under aerobic conditions have been published.[22] Furthermore, the crucial role of silica gel was further substantiated experimentally when an acetonitrile or acetone solution of brussonol (**33**) was stirred under oxygen atmosphere and only trace amounts of przewalskin E (**32**) were obtained after several days.

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

The formation of such a reactive quinone methide from *o*-quinone **31** and aerobic catechol oxidation under comparable reaction conditions has already been reported by Burnell et al.[32] Brussonol (**33**) was first isolated from *Salvia brussonetii* and shows insecticidal and anti-P388 leukemia cell activity. The spectral data of **33** gave good agreement with those reported for the natural and synthetic products.[13c,30b] The spectral data of quinone **32**, first synthetically prepared from natural demethylsalvicanol[30b] and subsequently isolated from *Salvia przewalskii MAXIM*,[33] correspond perfectly with those of the synthetic material, but significantly deviate 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 match those of our synthetic substance, the ^{1}H NMR chemical shifts (0.01–0.08 ppm) and FTIR absorption bands (the main signal at 1660 cm^{-1} was not reported and the signals at 1722 and 1680 cm^{-1} were found with much lower intensity) significantly diverge 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 *o*-quinones. Unfortunately, the authors did not compare their sample with the synthetic compound of Takeya and co-workers.[30b] However, the structure of **32** could be verified by converting it into brussonol (**33**) in excellent yield (94%) by reduction with aqueous $Na_2S_2O_4$. The resulting **33** was then oxidized back to **32** following the Takeya protocol (DDQ, dioxane).[30b] As the preparation of the proposed structure of **32** failed to produce a compound that could be identified as the natural product, as judged by different data, we propose that a structural reassignment of przewalskin E is necessary.

Synthesis of the proposed structure of dimeric C_{40} terpenes obtusinones D and E—reassignment of the configuration of obtusinone D

Having strong experimental evidence for the structure of synthetic **32** (by reduction to known brussonol (**33**) and subsequent re-oxidation), the unusual dimeric icetexanes obtusinones D (**34**) and E (**35**) were next synthesized (Scheme 9). The first reported example of such an icetexane dimer was grandione, which was isolated by Riccio and co-workers in 1999 from *Toreya grandis*[34] and synthesized by Takeya and co-workers in 2005 (and the structure was reassigned)[35] by solid-state

hetero-Diels–Alder dimerization of *o*-quinone **31**. Obtusinones D (**34**) and E (**35**), which were recently isolated by Salae and Boonnak, were suggested to originate biogenetically from a similar Diels–Alder dimerization of przewalskin E (**32**).[36] Having **32** in hand, modified Takeya conditions (neat, 100 °C, 6 h) were applied to achieve the first synthesis of both obtusinones D (**34**) and E (**35**) (1.7:1.0) in high overall yield (69%). The separation of the two synthesized natural products proved to be difficult by either flash chromatography or preparative TLC on silica gel utilizing the eluent reported in the isolation study.[36] We expected that π stacking of the two natural products could be responsible for the identical retention times. Consequently, we decided to change our eluent system by adding toluene to our solvent mixture to break the π-stacking interaction between **34** and **35**. Gratifyingly, the synthetic compounds were then successfully separated by preparative TLC after optimization of the eluent (pentane/toluene/Et_2O, 5:5:1). The spectral data of the two synthesized natural products were in perfect agreement with the natural samples. However, an X-ray analysis of a single crystal of obtusinone D (**34**, Figure 3) was performed and the structure shows opposite

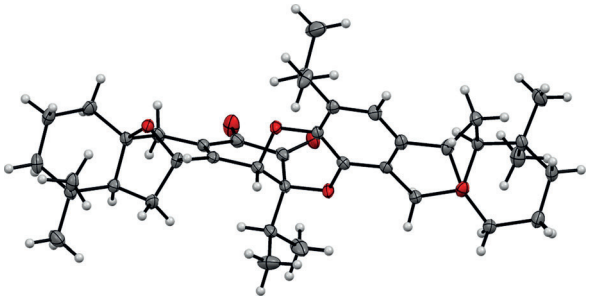


Figure 3. X-ray crystallographic structure of **34**. Red = oxygen, grey = carbon, white = hydrogen.

configurations at C13 and C14 to those reported by Salae and Boonnak.[36] Indeed, they assigned the configurations at C13 and C14 of **34** on the basis of 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[36] between these two centers. This NOESY correlation was later observed by us, therefore further substantiating the identity of our synthetic obtusinone D as the natural product.

The X-ray crystallographic analysis of synthetic obtusinone D in combination with the matching spectral data of both the 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 4B). Consequently, the configurations of C13 and C14 in obtusinone E are suggested to be identical to those of obtusinone D, as shown for the revised structure **37** (Figure 4B).

The different ratio of the isolated natural products (**36**/**37**, 4:1) detected compared with that 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.

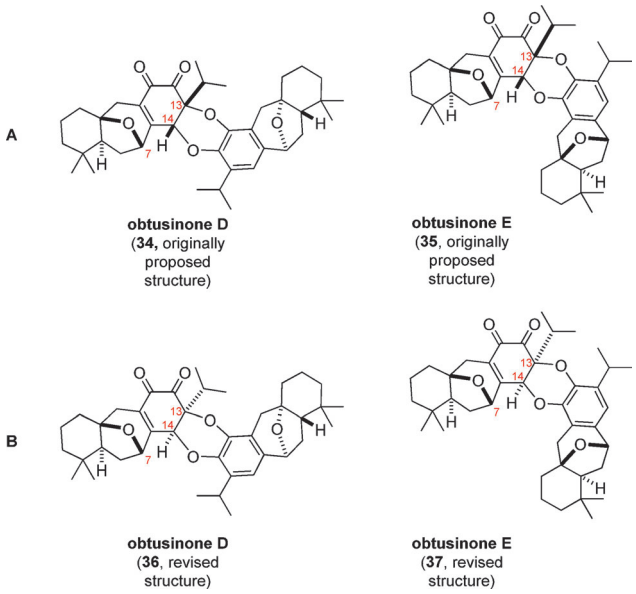


Figure 4. A) Originally proposed, and B) revised structures of obtusinones D and E.

Conclusions

A divergent, elegant, and short synthesis of 10 members of the icetexane family of natural products has been achieved in four to nine steps from abundant (+)-carnosic acid, isolated from *Rosmarinus officinalis*. Of these icetexanes, (+)-salvicanol (**12**), (−)-cyclocoulterone (**1**), (−)-coulterone (**22**), (−)-obtusinone D (**36**), and (−)-obtusinone E (**37**) have been synthesized for the first time. A straightforward, inexpensive, and efficient sequence, consisting of the methylation and hydrogenation of rosemary ethanol extracts enriched with carnosic acid and related congeners, has been developed to obtain the desired trimethyl carnosic acid **8** in high yield. The 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 10-hydroxy group. This is the first experimental evidence for the trapping of a tertiary carbocation, such as **5**, by a water molecule and a selective aromatic demethylation. (+)-Salvicanol (**12**) was used as a common intermediate to synthesize 1) (−)-brussonol (**33**) and the reported structure of (−)-przewalskin E (**32**) in two steps by an aromatic oxidation to form the *o*-quinone **31**, followed by an aerobic silica gel based tautomerization and oxidation, 2) (−)-obtusinone D (**36**), which was structurally reassigned, and (−)-obtusinone E (**37**) through hetero-Diels–Alder reaction of (−)-przewalskin E (**32**), 3) (+)-komaroviquinone (**2**) by a selective benzylic oxidation and an aromatic oxidation, 4) (−)-cyclocoulterone (**1**) and (+)-komarovispirone (**3**) by photolysis of (+)-komaroviquinone (**2**) in sunlight, which supports our previous hypothesis for the non-enzymatic biogenetic formation of methylenedioxy catechol nat-

ural products, and finally, 5) (−)-coulterone (**22**) through the hydrogenation of (+)-komaroviquinone (**2**).

Experimental Section

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

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Keywords: C–H activation · Diels–Alder reactions · natural products · reaction mechanisms · ring expansion

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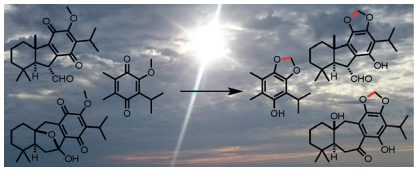
FULL PAPER

Let the sun shine in! A collective synthesis of ten icetexane natural products has been completed based on several biogenetic hypotheses. Of these icetexanes, (−)-cyclocoulterone was synthesized from (+)-komariviquinone by a redox-neutral C–H activation triggered by sunlight (see figure).



Natural Products

*C. Thommen, M. Neuburger, K. Gademann**

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Collective Syntheses of Icetexane Natural Products Based on Biogenetic Hypotheses