Biomimetic Synthesis

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Biomimetic Synthesis of Meroterpenoids by Dearomatization-Driven Polycyclization

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Abstract: *A biomimetic route to farnesyl pyrophosphate and dimethyl orsellinic acid (DMOA)-derived meroterpenoid scaffolds has yet to be reported despite great interest from the chemistry and biomedical research communities. A concise synthetic route with the potential to access DMOA-derived meroterpenoids is highly desirable to create a library of related compounds. Herein, we report novel dearomatization methodology followed by polyene cyclization to access DMOA-derived meroterpenoid frameworks in six steps from commercially available starting materials. Furthermore, several farnesyl alkene substrates were used to generate structurally novel, DMOA-derived meroterpenoid derivatives. DFT calculations combined with experimentation provided a rationale for the observed thermodynamic distribution of polycyclization products.*

Meroterpenoids derived from 3,5-dimethylorsellinic acid (DMOA) and farnesol pyrophosphate (FPP) comprise an extensive family of natural products containing a wide array of structural diversity and biological activity (Figure 1 a).[1] Over 100 congeners have been isolated and characterized, including tropolactone D (**1**),[2] berkeleyone A (**2**) (anti-inflammatory activity),[3] preterretonin A (**3**),[4] asperterpene A (**4**) (a potent BACE-1 inhibitor),[5] terretonins (antimicrobial),[6] austins,[7] andrastins,[8] preandiloid A (**5**),[9] and anditomin (**6**).[10] Despite the promising therapeutic potential of this family, many compounds remain untested or the biological assays are limited in scope, largely due to the small quantities of natural samples available via isolation methods. Although recent elegant syntheses of the DMOA-derived meroterpenoid family members berkeleyone A (**2**) and select andrastin/terretonin congeners have been reported by the Maimone and Newhouse laboratories,[11] a general biomimetic strategy to access the majority of DMOA/FPP natural product family remains elusive.

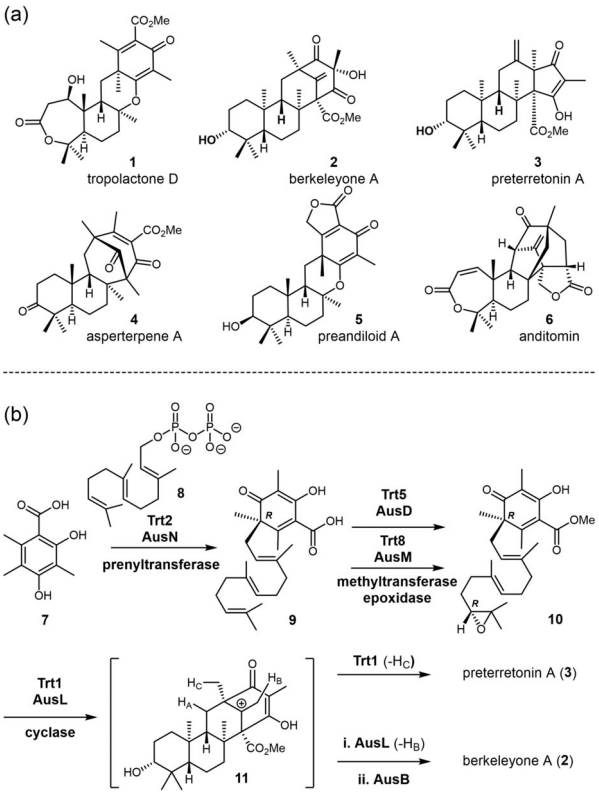

Figure 1. a) Representative DMOA-derived meroterpenoid natural products. b) Biosyntheses of the DMOA-derived meroterpenoids.

Studies on the biosyntheses of DMOA-derived meroterpenoids by the Abe laboratory[1,4,9,10,12] reveal, remarkably, that the broad spectrum of structural diversity exhibited within the natural product family is the result of divergent pathways from a common intermediate, **10** (Figure 1 b) and its stereoisomers.[1] For example, enzymatic pathways for natural products berkeleyone A (**2**) and preterrotonin A (**3**) have been rigorously established (Figure 1 b).[4,12a,b] In these sequences, DMOA (**7**) is first dearomatized with farnesyl

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pyrophosphate (**8**) and the resultant enzymatic intermediate **9** is methylated and subsequently epoxidized at the 10,11-trisubstituted alkene. Consequently, the dearomatized intermediate **10** is then accepted as a substrate by the terpene cyclase enzymes AusL and Trt1 which mediate cascade polycyclizations to form tetracyclic products berkeleyone A (**2**) and preterrotonin A (**3**) via cationic intermediate **11**. Thus, a biomimetic route is highly desirable to create a platform to generate numerous FPP/DMOA-derived meroterpenoids through a single and direct synthetic route.

Considering the biosynthetic pathway, we devised a synthetic scheme to access the key dearomatized substrate **14** which contains **10** as well as its stereoisomers (Figure 2).

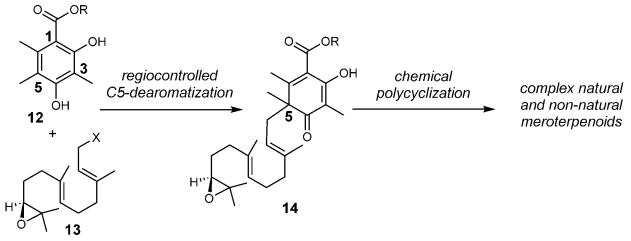
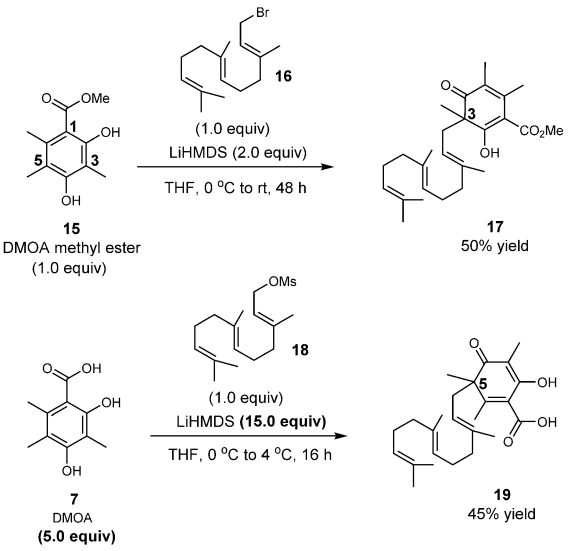


Figure 2. Biomimetic approach to access DMOA-derived meroterpenoids.

Intermediate **14** may be derived from dearomatization of DMOA (**7**) or derivatives **12** with an appropriate farnesyl electrophile **13** and serves as a gateway intermediate to access FPP/DMOA-derived meroterpenoids. However, achieving this site-selective dearomatization has proved extremely difficult to date using established base-mediated acylphloroglucinol dearomatization methodology.[13] A major challenge in our biomimetic approach lies in the ability to achieve C5-selective alkylative dearomatization of substrates **12** and suppress etherification of the phenols. Alkylative dearomatization of orsellinic acid derivatives has been achieved previously, but typically on C3 (cf. Figure 2).[13f] Following dearomatization, we propose that cationic epoxy-diene polycyclization [14] of **14** may be utilized to generate tetracyclic meroterpenoid products. Termination of the polyene cyclization is possible by either *C*-[11b,15] or *O*-cyclization[16] of the dearomatized enol moiety to produce asperterpene and preandiloid A-type scaffolds, respectively. To the best of our knowledge, this is the first report wherein the terminating group in a polyene cyclization is a pendant, dearomatized moiety. This unique terminating group provides a novel research area in the field of polyene cyclizations. Here, we report the first biomimetic approach to FPP/DMOA-derived meroterpenoids via novel dearomatization methodology followed by polycyclization that we term dearomatization-driven polycyclization (DDP). Tetracyclic meroterpenoids are constructed in six steps from commercially available materials (longest linear sequence) and allow access to the family of FFP/DMOA-derived meroterpenoids.

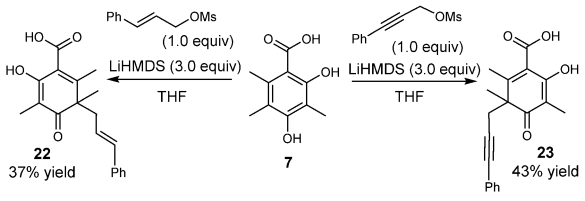
In our initial studies, we evaluated dearomative farnesylation of dimethyl atratate (DMOA methyl ester)[18] **15** under basic conditions[13d,h,i] (Scheme 1). Deprotonation of **15** with



Scheme 1. Ester-to-acid functional group conversion alters alkylative dearomatization regioselectivity.

LiHMDS in THF (0 °C) followed by reaction with farnesyl bromide **16** led to highly selective dearomative alkylation of **15** at the C3-position to afford **17** in 50 % yield. Alkylation of unsaturated carboxylic acids is known to occur at the (γ) position under basic conditions.[19] We considered whether the carboxylic acid **7** could undergo a similar C5, γ-selective alkylation. In the event, deprotonation of **7** with LiHMDS in THF to afford a lithium trianion[20] followed by alkylation with farnesyl mesylate **18** afforded only the desired regioisomer **19** in 45 % yield. The structure of **19** was identical to a natural sample of farnesyl DMOA isolated in the Abe laboratory.[12a] Moreover, additional experiments were conducted with cinnamyl and phenyl propargyl mesylate to extend the C5-alkylative dearomatization methodology to non-farnesyl electrophiles (Scheme 2).[21]

Our rationale for the alkylative dearomatization selectivity of methyl ester **15** vs. acid **7** is shown in Figure 3. Deprotonation of **15** with LiHMDS may afford the dienolate intermediate **20** which undergoes (α)-alkylation with **16** to afford the C3-dearomatized product **17**. The change in dearomatization selectivity of DMOA **7** is believed to arise via formation of the proposed dienediolate [19] intermediate **21** (Figure 3). (γ)-Alkylation of **7** with farnesyl electrophile **18** leads to the C5-dearomatized product **19**. After experimentation,[21] it was hypothesized that an aggregated species[22] is likely responsible for the regioselective dearomatization



Scheme 2. C5-dearomatization of **7** with cinnamyl and propargyl electrophiles.

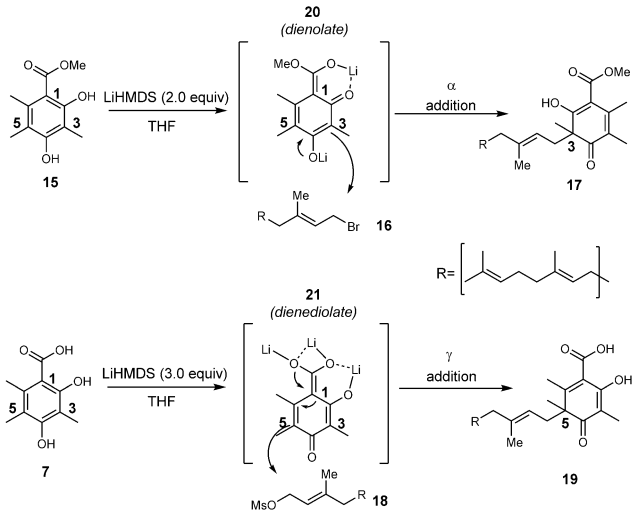
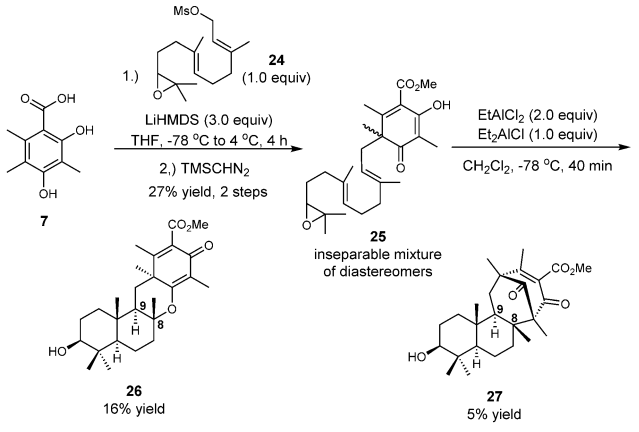


Figure 3. Rationale for C5 vs. C3 dearomatization.

outcome for **7**. The reaction was optimal at a concentration of 50 mM; use of higher or lower concentrations had a deleterious effect on the yield of **19**. We also discovered that the presence of salts and additives (e.g. LiCl, HMPA) led to a pronounced reduction in the yield of **19**. An improved yield of **19** was realized with use of an excess of DMOA trianion at 50 mM and a dilute (10 mM) concentration of **18**. By using an excess of DMOA trianion, the lithium mesylate salt concentration was effectively lowered, thereby allowing for an increase in the selectivity towards C5-dearomatization.

After dearomatization method development, we conducted a related dearomatization of **7** under basic conditions using (2*E*,6*E*)-10,11-epoxyfarnesyl mesylate (**24**) as electrophile (Scheme 3). After reaction completion, esterification of the crude product with TMS-diazomethane to access **25** was performed without isolation of the carboxylic acid. In particular, the intermediate acid proved to be incompatible with the epoxide on the farnesyl fragment leading to degradation when isolation was attempted.[21] The newly formed (2*E*,6*E*)-10,11-epoxyfarnesyl-5-dimethylorsellinic acid methyl ester (**25**) was isolated and characterized as a 1:1 mixture of diastereomers in 27% yield (2 steps).



Scheme 3. Dearomatization and polyene cyclization of (2*E*,6*E*)-10,11-epoxyfarnesyl-5-DMOA methyl ester (**25**).

Polyene cyclization has been found to be an expedient approach to quickly generate complex carbocyclic structures.[14,17,23] Literature reports[16b,24] have also shown that the traditional chair–chair transition state can be altered to a chair–boat assembly based on suitable modification of the polyene fragment or terminating group. Our experimental results revealed that the dearomatized intermediate **25** was highly prone to rearomatization under acidic conditions to afford DMOA methyl ester **15**.[21] After considerable experimentation, we found that alkyl aluminum-based Lewis acids (e.g. Et_2AlCl, $EtAlCl_2$, and $MeAlCl_2$) were the only initiators that could perform the polyene cascade cyclization to afford fully cyclized tetracyclic meroterpenoids. Ultimately, we found that a mixed Lewis acid combination of 2:1 $EtAlCl_2$:Et_2AlCl as a mediator afforded the best results.[17,23c] After cyclization of substrate **25** was complete, two fully cyclized compounds **26** and **27** were isolated (Scheme 3). Both compounds are derived from different diastereomers of dearomatized intermediate **25** and from the corresponding Stork–Eschenmoser[25] chair–chair transition states (Figure 4a). The *C*-cyclized compound **27** contains the (8,9)-*epi*-

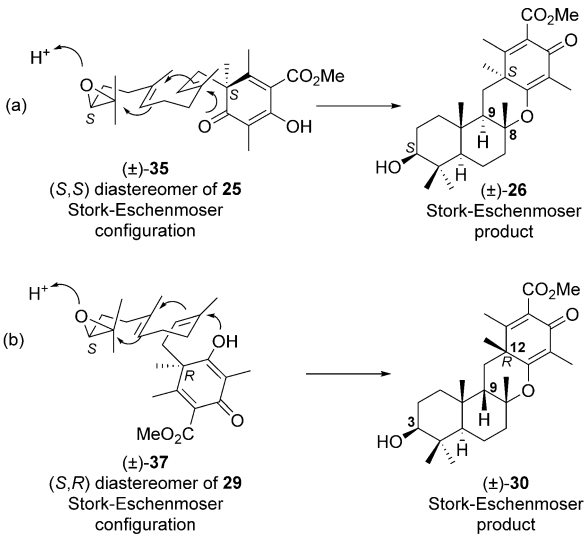
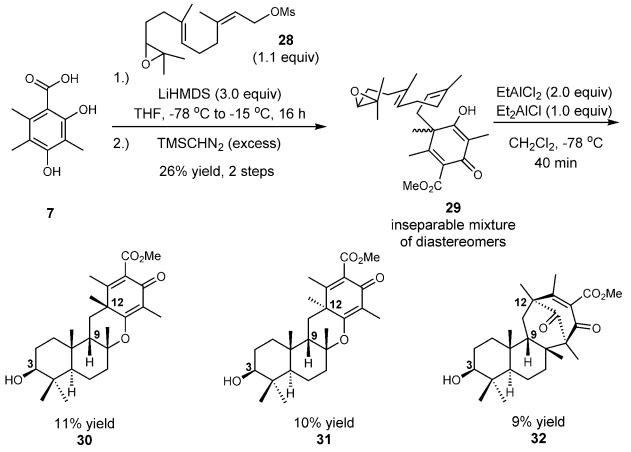


Figure 4. Product predictions based on Stork–Eschenmoser configurations.

asperterpene skeleton and the *O*-cyclized product **26** contains the (8,9)-*epi*-tropolactone D skeleton (cf. Figure 1a). The structures of **26** and **27** were determined by 2D NMR analysis and compound **26** was fully confirmed by X-ray crystallography[26] using the crystalline sponge (CS) method which has been successfully used to determine structures of non-crystalline terpenoids.[27]

We hypothesized that if a (2*Z*,6*E*)-(10,11)-epoxyfarnesyl-5-dimethylorsellinic acid methyl ester (**29**) substrate variant was used, the opposite stereochemistry[28] at C9 should be obtained based on Stork–Eschenmoser configurations (cf. Figure 4b). The synthesis of **29** also employed alkylative dearomatization of the lithium trianion derived from DMOA

7 with (2*Z*,6*E*)-10,11)-epoxyfarnesyl mesylate (**28**) and was found to require a lower temperature (−15 °C) (Scheme 4). It is apparent that the (2*Z*)-alkene geometry of substrate **29** generates a more readily rearomatized substrate leading to elimination on the farnesyl chain.



Scheme 4. Dearomatization and polyene cyclization of (2*Z*,6*E*)-(10,11)-epoxyfarnesyl-5-DMOA methyl ester (**29**).

(2*Z*,6*E*)-(10,11)-Epoxyfarnesyl-5-dimethylorsellinic acid methyl ester substrate (**29**) (1:1 mixture of diastereomers) was then exposed to polyene cyclization conditions using $EtAlCl_2$/Et_2AlCl (2:1). Three fully cyclized compounds were isolated which are all derived from Stork–Eschenmoser-type transition states (*cf.* Figure 4b) and bearing the opposite stereochemistry at C9 as expected. Meroterpenoid **30**, an 8-*epi*-preandiloid A type framework (cf. Figure 1a), is the only compound derived from the (3*S*,12*R*) diastereomer of **29**. Both *O*- and *C*-cyclized products **31** and **32** are derived from the same (3*S*, 12*S*) diastereomer of **29**. The structure of **30** was determined by 2D NMR analysis and the structures of both **31** and **32** (the latter as the derived *p*-bromobenzoate derivative) were determined by X-ray crystal structure analysis (Figure 5).[26]

Of the possible eight fully cyclized structures that may be produced with Stork–Eschenmoser configurations, only five structures were generated from chemical polycyclization (cf. Schemes 3 and 4). DFT analysis of the products (B3LYP-D3(BJ)/6-31G**)[29] showed that the isomers have a range of relative energies. In each case, the lower energy terminating group (O vs. C) is produced as the isolated product, except for substrate **39** (*S*,*S* diasteromer of **29**) which results in production of both *O*- and *C*-cyclized products **31** and **32** (vide infra Figure 6). We note that all products generated from chemical cyclizations obey the Stork–Eschenmoser hypothesis (cf. Figure 4) wherein the conformation of the product is adopted by the substrate prior to polycyclization.[25]

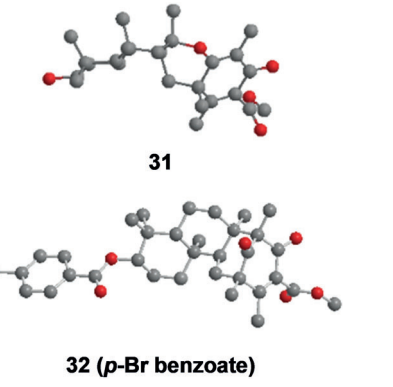


Figure 5. X-ray crystal structures of DMOA-derived meroterpenoids **31** and **32** (*p*-Br benzoate).

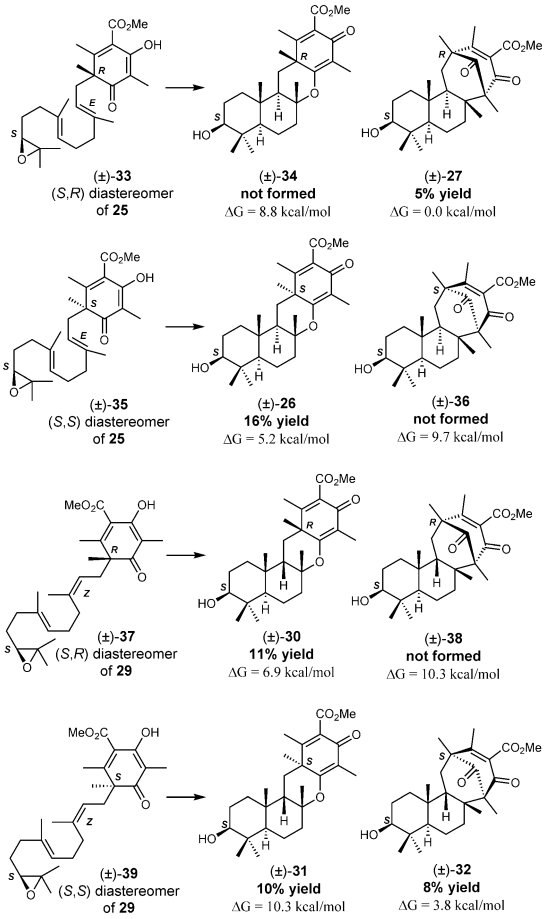
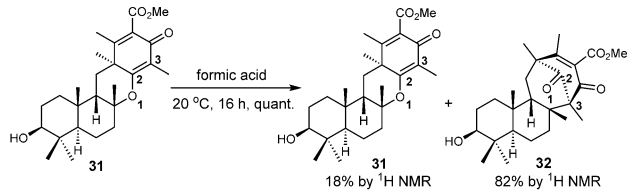


Figure 6. B3LYP-D3(BJ)/6-31-G** relative energy (kcal mol^{-1}) levels for fully cyclized products.

Based on analysis of the product energies (Figure 6), we considered whether *O*-cyclized products such as **31** may undergo [1,3] *O-to-C* rearrangement.[30] Indeed, when **31** was stirred in neat formic acid,[13d] a mixture of **31** and **32** was observed, confirming [1,3] shift reactivity (Scheme 5). This result demonstrates that thermodynamic equilibration to an energetically favored cyclization product such as **32** may occur. On the other hand, subjection of *O*-cyclized product **30** to acidic conditions[21] did not produce cyclized products such as **38** which has a correspondingly high relative DFT energy.

In conclusion, we have successfully demonstrated regioselective, biomimetic C5-dearomatization of 3,5-dimethylorsellinic acid (DMOA) with farnesyl derivatives and other



Scheme 5. Formic acid-catalyzed [1,3] *O*-to-*C* rearrangement.

electrophiles under basic conditions. Dearomatization-driven polycyclization (DDP) of the key dearomatized epoxyfarnesyl-5-dimethylorsellinic acid methyl ester scaffolds was conducted generating unique tetracyclic, DMOA-derived meroterpenoids. Product outcomes of *O* vs. *C* termination in polycyclizations were probed by DFT computation and experiments showing thermodynamic equilibration of products via [1,3] *O-to-C* rearrangement. Further studies on the chemical and chemoenzymatic synthesis of meroterpenoids and derivatives as well as biological and computational studies are currently in progress and will be reported in due course.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: 3,5-dimethylorsellinic acid · biosynthesis · dearomatization · meroterpenoids · polyene cyclization

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Communications

Biomimetic Synthesis

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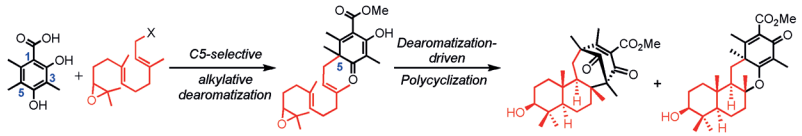
Biomimetic Synthesis of Meroterpenoids by Dearomatization-Driven Polycyclization



Regioselective dearomatization of 3,5-dimethylorsellinic acid (DMOA) provides rapid access to a key dearomatized intermediate in the biosynthetic pathway of DMOA-derived meroterpenoids. This intermediate undergoes polycyclization under Lewis acid mediation to provide meroterpenoid scaffolds. Several structurally novel meroterpenoids were obtained by termination via either *C*- or *O*-cyclization.