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Total Synthesis and Assignment of the Absolute Configuration of (+)-Omphalic Acid

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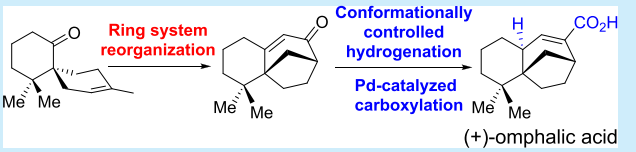
ABSTRACT: Omphalane diterpenoids usually contain a cyclohexane-fused bicyclo[3.2.1]octane scaffold embedded with two continuous quaternary carbon centers, which pose considerable challenges to synthetic chemists. Herein, we reported the first total synthesis of omphalic acid with high stereochemical control, featuring an intermolecular Diels–Alder cycloaddition, ring reorganization through Criegee oxidative cleavage and programmed aldol condensations, conformationally controlled hydrogenation, and Pd-catalyzed carboxylation. The absolute configuration of omphalic acid was defined for the first time via the asymmetric total synthesis facilitated by a derivatization resolution protocol.



Omphalane sesquiterpenoids are a small group of secondary metabolites containing a cyclohexane-fused bicyclo[3.2.1]octane scaffold embedded with two continuous quaternary carbon centers (C_4 and C_5), which have been identified in both terrestrial and marine organisms, such as omphalic acid (**1**)[1] from liverworts, dactylomelatriol (**2**)[2] from sea hare, and güimarediol (**3**)[3] and omphalaurediol (**4**)[4] from red algae (Figure 1). Interestingly, the *cis*- and *trans*-fusion

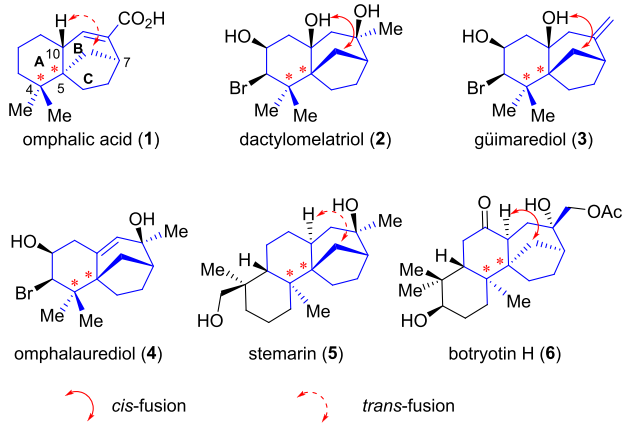


Figure 1. Selected terpenoids containing omphalane carbon skeletons.

patterns both occur in these natural products. For example, compound **1** has a *trans*-fused 6/7 backbone, while compounds **2** and **3** have a *cis*-fused 6/7 backbone. Notably, similar carbon skeletons are also found in stemarane and betaerane diterpenoids,[5] such as stermarin (**5**)[6] and botryotin H (**6**).[7] Biosynthetically, starting from the universal acyclic precursor farnesyl diphosphate, omphalane sesquiterpenoids are formed presumably through a chamigrane-type[8] intermediate by a cyclization, ring contraction, and cyclization process.[1]

As the first discovered omphalane sesquiterpene, omphalic acid (**1**) was isolated from the Colombian liverwort *Omphalanthus filiformis* in 1995 by Asakawa and co-workers.[1] The tricyclic structure of compound **1** was determined by spectroscopic analysis of its methyl ester derivative. Nevertheless, the absolute configuration was not determined. Together with its marine relatives compounds **2**–**4**, these sesquiterpenes constitute a natural product family bearing structurally challenging carbon skeletons and diverse oxidation levels and, thus, are intriguing targets for synthetic chemists. To date, there is still no synthetic report for these molecules. As part of our continuing interest in developing novel synthetic strategies toward bioactive terpenoids,[9] we herein report the first total synthesis of omphalic acid (**1**) with high stereochemical control. We also developed a concise and general synthetic approach to assemble the omphalane sesquiterpenoid skeletons containing either *trans*- or *cis*-fused 6/7 substructures. Furthermore, the absolute configuration of compound **1** was designated as (5*R*,7*R*,10*S*) for the first time through total synthesis.

Our retrosynthetic analysis is depicted in Scheme 1. We envisioned that omphalic acid (**1**) could be accessed from tricyclic ketone **7** through enol triflate formation and subsequent Pd-catalyzed carboxylation. As the central

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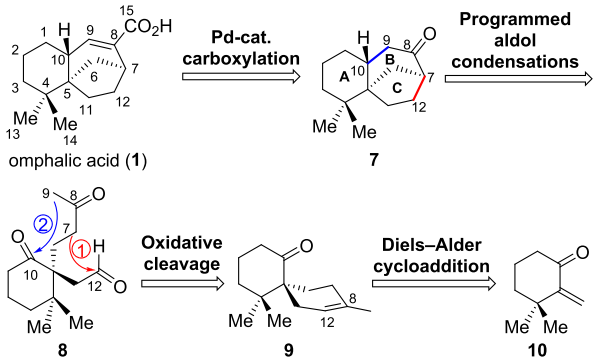
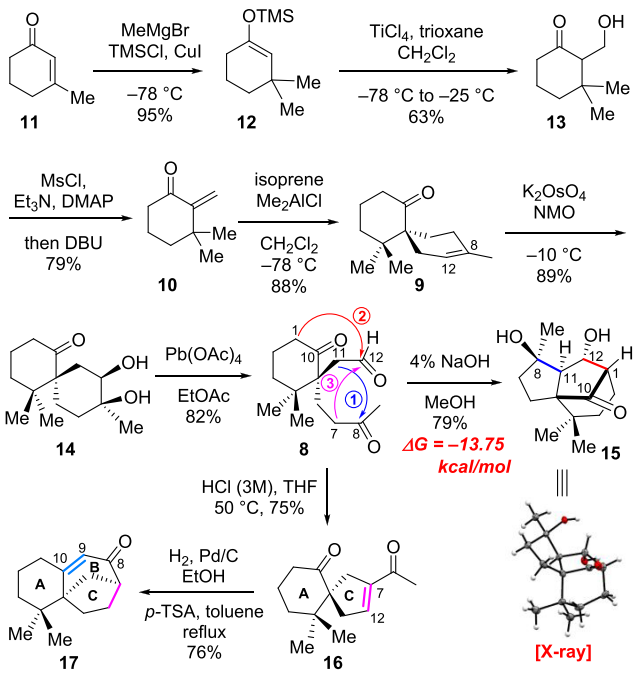
Scheme 1. Retrosynthetic Analysis of Omphalic Acid (1)



challenge, the stereoselective construction of the tricyclic skeleton of compound **1** could be tackled by programmed aldol condensations from the tricarbonyl precursor **8**. This ring-formation strategy was later proven to be a bold design on a versatile substrate bearing four types of acidic α protons of three carbonyl groups. The tricarbonyl compound **8** could arise from enone **9** via oxidative cleavage of the C_8–C_{12} double bond. Finally, the spirobicyclic compound **9** could be obtained from α,β-unsaturated enone **10**[10] and isoprene through intermolecular Diels–Alder cycloaddition.

Our synthetic endeavors commenced with a concise preparation of enone **10**, which has been previously synthesized in six steps[10,11] (Scheme 2). Through a newly

Scheme 2. Synthesis of Intermediate 17



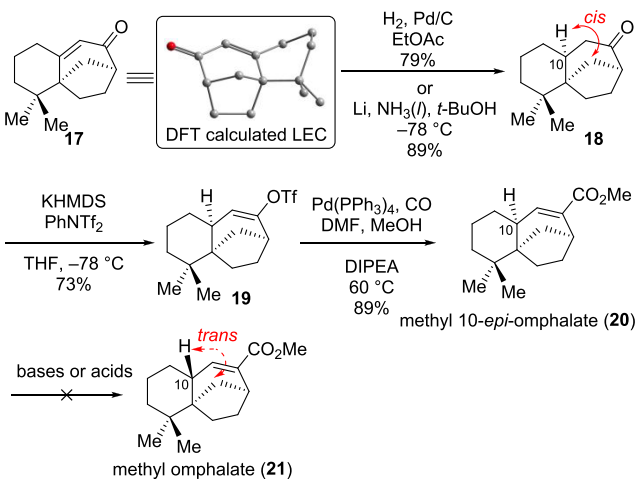
developed three-step synthetic sequence including conjugate addition, Mukaiyama aldol reaction, and dehydration, compound **10** could be prepared on a large scale. However, compound **10** was unstable and usually underwent dimerization through hetero-Diels–Alder reaction upon standing at room temperature overnight (see the Supporting Information for details). Instant treatment of compound **10** and 3.0 equiv of isoprene with an equimolar amount of Me_2AlCl at −78 °C afforded spirobicyclic enone **9** in 88% yield. Notably, usage of the catalytic amount of Me_2AlCl would lead to a significant amount of the dimeric product of compound **10**. Although preparation of tricarbonyl intermediate **8** via ozonolysis of compound **9** failed, the cleavage of the C_8–C_{12} double bond through dihydroxylation followed by Criegee oxidation[12] provided compound **8** in 73% overall yield.

Next, our investigation focused on the construction of the bicyclo[3.2.1]octane ring system (B–C rings). As mentioned above, as a result of the versatile reactivity of compound **8**, a well-orchestrated aldol reaction sequence is required. To our surprise, the initial attempt of the basic conditions with 4% aqueous NaOH in MeOH led to the formation of diol **15** in 79% yield, which also contains a bicyclo[3.2.1]octane ring (Scheme 2). The structure of compound **15** was verified unambiguously by X-ray crystallographic analysis. This unexpected product was derived from compound **8** probably through an abnormal cascade aldol reaction, involving the first aldol addition of C_{11} to C_8, followed by the second aldol addition of C_1 to C_{12}. The density function theory (DFT) calculation indicated that this cascade reaction is a thermodynamically favorable process, with ΔG = −13.75 kcal/mol (see the Supporting Information for details). To our delight, upon treatment with aqueous HCl (3 M), compound **8** was smoothly converted to the desired aldol condensation product **16** in 75% yield. Driven by curiosity, we subjected the unexpected product **15** to the above acidic conditions to see whether a transformation of compound **15** to compound **16** based on a retroaldol and aldol reaction sequence is possible. Unsurprisingly, compound **15** remained intact. Subsequent one-flask hydrogenation and aldol condensation delivered tricyclic enone **17** in 76% yield.

With compound **17** in hand, our next goal was the saturation of the C_9–C_{10} double bond. Unfortunately, whether hydrogenation with Pd/C under a H_2 atmosphere through a dynamically controlled manner or conjugate reduction with $Li/NH_3(l)$ and *t*-BuOH through a thermodynamically controlled way was employed, the undesired ketone **18** containing a *cis*-fused 6/7 backbone was produced as a single diastereomer (Scheme 3).

We attributed these failures to the unfavorable steric hindrance governed by a relatively rigid conformation of the substrate [see the inset in Scheme 3 for the DFT-calculated lowest energy conformer (LEC) of compound **17**] or the

Scheme 3. Synthesis of Methyl 10-*epi*-Omphalate (20)



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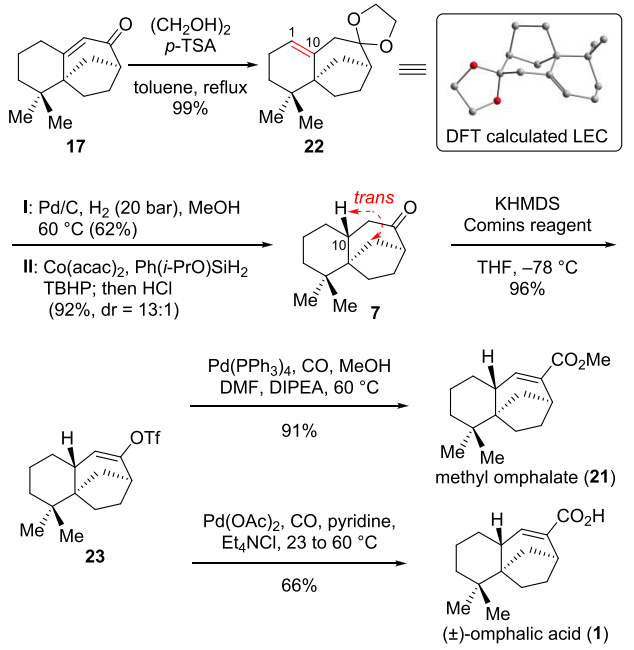
intermediate.[13] However, we anticipated that the C_{10} configuration could be reversed later by epimerization. To this end, compound **18** was converted to enol triflate **19**, which then underwent Pd-catalyzed carboxylation[14] to deliver methyl 10-*epi*-omphalate (**20**) in 65% overall yield. To epimerize the C_{10} stereocenter, we tried many different tactics, such as the deprotonation−protonation process with either basic (DBU, MeONa, or KHMDS) or acidic (*p*-TSA) conditions and the reversible radical epimerization with benziodoxole azide and H_2O developed by Chen et al. recently.[15] Unfortunately, none of them worked.

Bearing these lessons in mind, we envisioned that a dramatic conformational change of the tricyclic skeleton might facilitate the desired diastereoselective hydrogenation.[13] To this end, compound **22** was selected as a substrate for the hydrogenation, which could be prepared from compound **17** through a ketalization−isomerization cascade (Scheme 4). As shown by

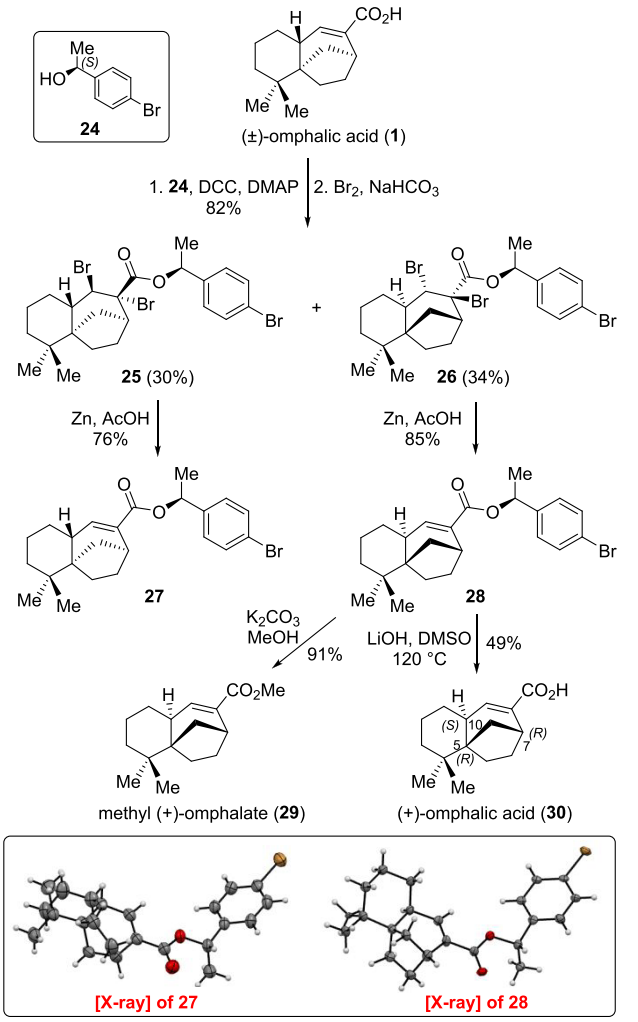
Scheme 4. Total Synthesis of (±)-Omphalic Acid



the DFT-calculated LEC, the hydrogenation was expected to predominantly occur from the less hindered *β* face of the C_1−C_{10} olefin to yield compound **7**. Gratifyingly, upon treatment of compound **17** with Pd/C and H_2 (20 bar) at 60 °C, the desired ketone bearing a *trans* 6/7-fused ring system (**7**) was obtained in 62% yield as a single diastereomer. We also found that Co-catalyzed HAT hydrogenation[16] could deliver compound **7** in 92% yield [diastereomeric ratio (dr) = 13:1]. Then, compound **7** was smoothly converted to enol triflate **23** in 96% yield. Finally, Pd-catalyzed carboxylation[17] furnished (±)-omphalic acid (**1**) in 66% yield as a racemate. The structure of compound **1** was confirmed by comparing the spectroscopic data of its methyl ester derivative (**21**) to the reported data, except for the optical rotation.

The originally proposed configuration[1] of omphalic acid was unexpected because related omphalane sesquiterpenoids, such as dactylomelatriol (**2**), güimarediol (**3**), and omphalaurediol (**4**), had opposite configurations at C_5 and C_7. To further assign the absolute configuration, the racemic synthesis described above could serve as a starting point. The racemic omphalic acid (**1**) was resolved by derivatizing with (*S*)-1-(4-bromophenyl)ethan-1-ol (**24**) (Scheme 5). Esterification of

Scheme 5. Enantioselective Synthesis and Assignment of Absolute Configuration



compound **1** with compound **24** using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) afforded an inseparable mixture of diastereomers (**27** and **28**) in 82% yield.

To further separate these two diastereomers, a two-step manipulation including dibromination−separation−reductive debromination was carried out. Gratifyingly, dibromide compounds **25** and **26** were readily separated by preparative thin-layer chromatography in 30 and 34% yield, respectively (see the Supporting Information for details). Reductive debromination with Zn and AcOH delivered esters **27** and **28**, whose configurations were confirmed by X-ray crystallographic analysis. To our great delight, methanolysis of compound **28** in the presence of K_2CO_3 delivered methyl (+)-omphalate (**29**), whose spectroscopic data and optical rotation {synthetic, $[\alpha]_D^{22}$ +58.4 (*c* = 0.8 in $CHCl_3$); natural, $[\alpha]_D^{22}$ +74.5 (*c* = 1.14 in $CHCl_3$)} are in accordance with the data published by Asakawa et al.[1] In addition, similar manipulation on compound **27** provided methyl (−)-omphalate (see the Supporting Information for details). Hydrolysis of compound **28** with LiOH in dimethyl sulfoxide (DMSO)

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afforded (+)-omphalic acid **30** in 49% yield. These results led to the assignment of the absolute configuration of natural (+)-omphalic acid as 5*R*,7*R*,10*S*, which also indicates that the absolute configurations of C_5 and C_7 of (+)-omphalic acid are in line with those of omphalane sesquiterpenoids **2**−**4**.

In summary, we reported the first total synthesis of (±)-omphalic acid in high stereochemical control, which resulted in the conformation of its relative configuration. An enantioselective synthesis of (+)-omphalic acid, combined with X-ray structures, led to the assignment of the absolute configuration of the natural product.[18] The key transformations in the synthetic route include an intermolecular Diels−Alder cycloaddition, ring reorganization through Criegee oxidative cleavage and programmed aldol condensations, conformationally controlled hydrogenation, Pd-catalyzed carboxylation, and derivatization resolution protocol. Furthermore, we developed a concise and general synthetic approach to assemble the omphalane sesquiterpenoid skeletons containing either *trans*- or *cis*-fused 6/7 substructures. The application of these synthetic technologies for the syntheses of other omphalane sesquiterpenes is undergoing in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02599.

Experimental procedures, characterization data, and NMR spectra for all products, X-ray crystallographic data for compounds **15** (CCDC 2090675), **27** (CCDC 2090676), and **28** (CCDC 2090674), computed energies, and Cartesian coordinates of all of the DFT-optimized structures (PDF)

Accession Codes

CCDC 2090674−2090676 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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