Total Synthesis

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Total Synthesis of (+)-Omphadiol**

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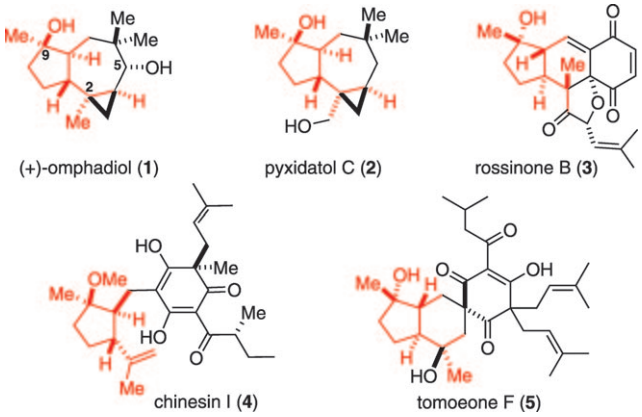
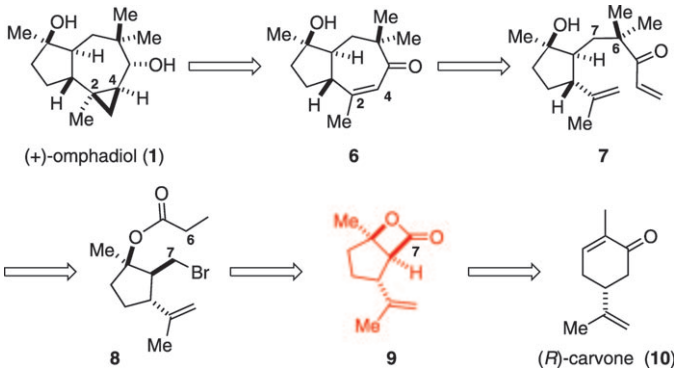
Omphadiol (**1**) is a sesquiterpene isolated from the basidiomycete *omphalotus illudens* and the edible fungus c*lavicorona pyxidata* (Scheme 1).[1] As a member of the africanane family



Scheme 1. (+)-Omphadiol and structurally related terpenes.

of sesquiterpenes, which all possess a 5-7-3 tricyclic core, omphadiol contains six contiguous stereogenic centers, which makes it a challenging synthetic target. Comparison with structurally similar terpenoids, including pyxidatol (**2**) and africanol (not shown),[2] reveals a large family of sesquiterpenes and diterpenes that share a common tetrasubstituted cyclopentane ring (highlighted in red). Notably, many of these natural products display potent biological activities. For example, rossinone B (**3**) shows anti-inflammatory, antiviral, and antiproliferative activities[3] while chinesin (**4**) possesses antimicrobial and antiviral activity.[4] Tomoeone F (**5**) displays significant cytotoxicity against KB cells.[5] While synthetic studies toward members of this family including a recent biomimetic synthesis of (±)-rossinone B have appeared,[6] no further biological studies have been described. Full biological evaluation of omphadiol was precluded owing to insufficient quantities isolated from natural sources.[1a] As part of a program to demonstrate the utility of β-lactones as synthetic intermediates, we set out to develop a scaleable route to the common cyclopentane core (highlighted in red) found in these terpenoids as a prelude to biological studies and investigations into their likely biosynthetic interconnectivity. Herein we report a three-step synthesis of a versatile, carvone-derived bicyclic β-lactone, which constitutes the key intermediate for the described ten-step synthesis of (+)-omphadiol. This total synthesis also features several efficient C–C bond-forming reactions, novel single-pot, sequential and tandem processes, and the highly stereocontrolled introduction of all six stereogenic centers.

Our synthetic strategy was premised on a late-stage facially selective cyclopropanation of the C2–C4 double bond governed by the topology of the [5.3.0] bicycle **6** (Scheme 2). The cycloheptenone would in turn be constructed



Scheme 2. Retrosynthetic analysis of (+)-omphadiol from (*R*)-carvone via the versatile bicyclic-β-lactone **9**.

by ring-closing metathesis (RCM) of diene **7**, which could be derived from bromide **8** by a sequential one-pot intra-/intermolecular dialkylation. The key intermediate for the synthesis of omphadiol and related terpenes was identified as the bicyclic β-lactone **9**. We anticipated that this versatile intermediate could be constructed by the reorganization of the carbon skeleton of (*R*)-carvone through a nucleophile-promoted aldol lactonization process of a derived keto acid.

The synthesis of (+)-omphadiol commenced with a $[Mn^{III}(dpm)_3]$-catalyzed (dpm = dipivaloylmethanato) formal hydration of the enone moiety of (*R*)-carvone to afford the hydroxy ketone **11** in a chemo- and regioselective manner and as an inconsequential mixture of diastereomers (d.r. 2:1; Scheme 3).[7] Subsequent oxidative cleavage of the α-hydroxyketone by periodic acid delivered ketoacid **12**. Upon activation of the carboxylic acid with tosyl chloride, and the addition of 4-PPY (4-pyrrolidinopyridine) as a nucleophilic promoter, ketoacid **12** underwent an aldol lactonization[8] to give the desired bicyclic β-lactone **9** with high diastereoselectivity (55%, d.r. > 19:1, as determined by ^{1}H NMR spectroscopy) after 24 hours, thus setting the first C–C bond (highlighted in red). Optimization studies revealed

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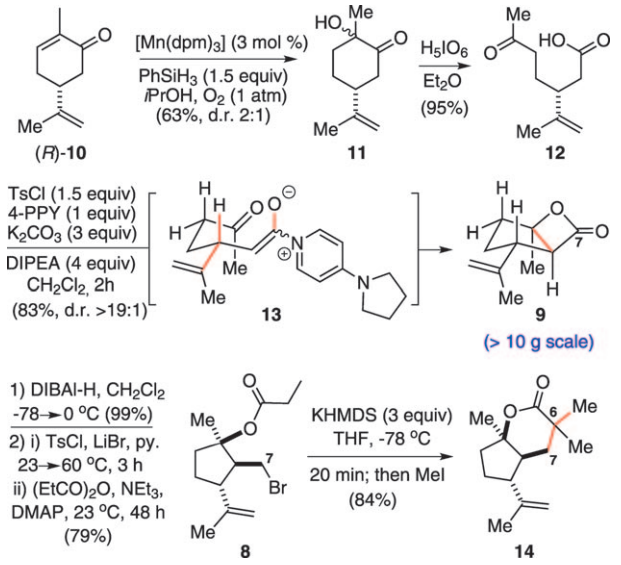
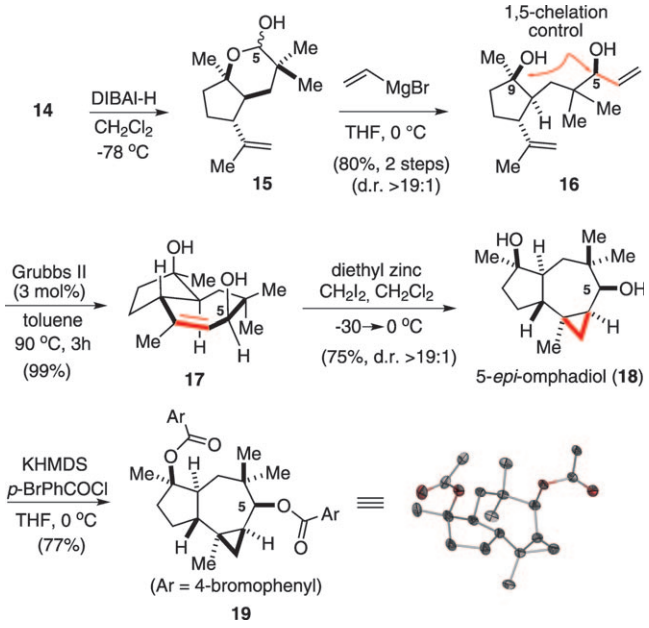


Scheme 3. Conversion of (*R*)-carvone into the versatile bicyclic-β-lactone **9** and bicyclic δ-lactone **14**. DIPEA = diisopropylethylamine, DIBAl-H = diisobutylaluminium hydride, DMAP = 4-dimethylaminopyridine, dpm = dipivaloylmethanato, HMDS = hexamethyldisilazide, PPY = 4-pyrrolidinopyridine, Ts = *p*-toluenesulfonyl.



Scheme 4. Synthesis of 5-*epi*-omphadiol (inset: ORTEP representation of the X-ray crystallographic structure of derivative **19**; aryl groups removed for clarity; thermal ellipsoids are shown at 50 % probability).[22] THF = tetrahydrofuran.

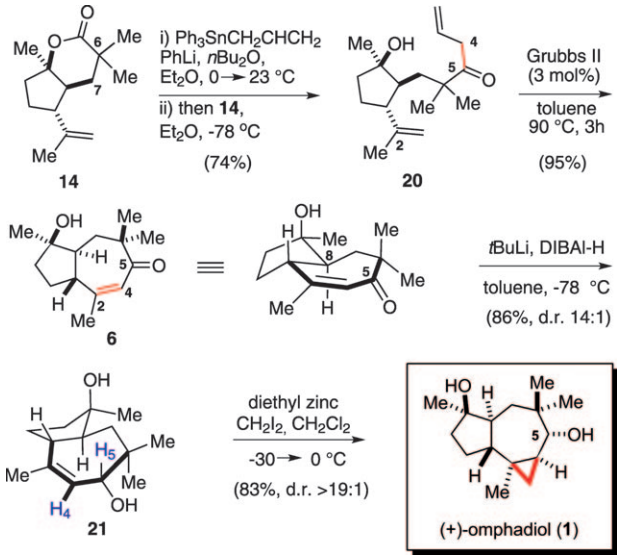
that powdered anhydrous K_2CO_3, in combination with iPr_2NEt as a shuttle base,[9] led to a high yield (83 %) of β-lactone **9** in 2 hours on a scale greater than 10 g. The high diastereoselectivity is rationalized by the chairlike transition state **13**, wherein the isopropenyl moiety adopts a pseudo-equatorial position to avoid 1,3-allylic strain with the ammonium enolate (*E*/*Z* geometry undefined) substituent and developing 1,3-diaxial interaction (bonds highlighted in red).

The next stage of the synthesis required a four-carbon homologation at C7, including the introduction of the C6-*gem*-dimethyl moiety. Reduction of the β-lactone **9** gave the corresponding diol that was converted into the corresponding C7-bromide (Scheme 3). After numerous failed attempts to form the C6–C7 bond using intermolecular alkylations with various nucleophiles, we considered intramolecular variants. Ultimately, a highly efficient process for construction of the C6–C7 bond was identified, which involved a one-pot tosylation/bromination sequence and a subsequent acylation to provide ester **8**. Treatment of this ester with KHMDS (3 equiv) in THF at −78 °C, followed by quenching with excess MeI, furnished the bicyclic δ-lactone **14** bearing the requisite C6 *gem*-dimethyl moiety. Thus, two required C–C bonds were formed in one operation. Notably, a dramatic and unusual counterion effect was observed in this transformation, since LHMDS and NaHMDS gave only O-alkylation products in the initial intramolecular alkylation.[10]

With ester **14** in hand, a two-step sequence involving the reduction to the lactol and vinyl Grignard addition was envisioned to introduce the remaining two carbon atoms required for the ring-closing metathesis (RCM) to form cycloheptene **17** (Scheme 4). While the degree of diastereoselectivity, if any, for the Grignard addition step was uncertain, ester **14** was reduced to lactol **15** by DIBAl-H, and to our surprise the subsequent addition of vinyl magnesium bromide gave diene **16** with high diastereoselectivity (d.r. > 19:1, as determined by ^1H NMR spectroscopy) even at 0 °C. The stereochemical outcome of this addition was confirmed following conversion into 5-*epi*-omphadiol (**18**) and by X-ray crystallographic analysis of ester **19**. One rationalization for this rare example of 1,5-stereoinduction[11] invokes chelation control between an in situ generated C9-magnesium alkoxide and the C5-aldehyde, thus leading to an eight-membered metallocycle that imparts substantial facial bias during nucleophilic addition. RCM of diene **16** using Grubbs second generation catalyst[12] yielded the desired *trans*-fused [5.3.0] bicyclic core in nearly quantative yield. A Simmons–Smith cyclopropanation of allylic alcohol **17** gave cyclopropane **18** with high diastereoselectivity (> 19:1). However, comparison with NMR data reported for the natural product suggested that a diastereomer had been produced. X-ray crystallographic analysis of the bis(*p*-bromophenylester) derivative **19** unambiguously determined that diol **18** was actually a C5 epimer of omphadiol. The high diastereoselectivity obtained during the vinyl Grignard addition unfortunately led to the unnatural C5 diastereomer but revealed an interesting example of 1,5-stereoinduction.

We recognized that one solution to the C5-stereochemical issue would involve a facially selective reduction of enone **6**, which can be derived from the RCM of a dienone (cf. **7**, Scheme 2). The seemingly straightforward conversion of the sterically hindered lactone **14** into enone **7** by the mono-addition of a vinylmetal species (e.g. vinyllithium, vinylmagnesium bromide, and divinylzinc), proved challenging. In contrast to the facile partial reduction to lactol **15** by DIBAl-H (Scheme 4) and numerous reported successful monoadditions of vinylmetal reagents to δ-lactones, the monoaddition

reaction with the sterically congested δ-lactone **14** was unsuccessful. The major by-product was derived from the subsequent 1,4-conjugate addition to the initially formed α,β-enone **7**.[13] Ultimately, this problem was circumvented by addition of allyllithium, derived from allyltriphenyltin[14] by transmetalation, to δ-lactone **14** to give the β,γ-enone **20** (Scheme 5). Use of the latter intermediate was premised on a designed tandem isomerization/RCM process guided by the known reluctance of RCM to provide eight-membered rings[15] and the ability of the ruthenium–hydride species generated from the Grubbs catalyst to promote olefin isomerization.[16] As predicted, upon heating diene **20** with the second generation Grubbs catalyst in toluene, the desired cycloheptenone was formed in 95% yield, thus indicating that olefin isomerization was faster than RCM, a situation which would have led to a cyclooctenone.



Scheme 5. Synthesis of (+)-omphadiol.

At this juncture, what remained to reach omphadiol was the regio- and stereoselective reduction of the enone and a facially selective cyclopropanation. After studying several reaction conditions, enone **6** was reduced smoothly to give the desired allylic alcohol **21** by treating with a DIBAl-H/*t*BuLi complex at −78 °C in toluene (d.r. 14:1).[17] Finally, the cyclopropanation of allylic alcohol **21** under Simmons–Smith conditions gave (+)-omphadiol with high facial selectivity (d.r. > 19:1). Despite the well-known directing effect of allylic alcohols in seven-membered rings under Simmons–Smith conditions,[18] this was not observed. This avoided the need for protection of the C5-hydroxy group. The unique conformational constraint of allylic alcohol **21**, imposed by the bicyclic structure, places the secondary hydroxy group in a pseudo-equatorial position (in plane with the π bond). This rigid conformation is likely responsible for the unexpected, non-hydroxy directed but desired facial selectivity.[19] Both DFT calculations[20] and NMR studies ($J_{H4,H5} = 0$ Hz) of alcohol **21** support the conformation shown in Scheme 5. Synthetic (+)-omphadiol correlated well spectroscopically with the natural product, including the optical rotation.

In summary, the first total synthesis of (+)-omphadiol has been achieved in ten steps from (*R*)-carvone in an 18% overall yield. This synthesis features the highly stereocontrolled introduction of the six contiguous stereogenic centers exclusively by using substrate control from the single stereocenter in (*R*)-carvone. The concise nature of the synthesis derives from a high ratio of C–C bond-forming steps (five of the ten steps) that proceed in a highly efficient manner, the design and implementation of novel single-pot sequential processes, and the absence of protecting groups.[21] This total synthesis paves the way for further biological studies of omphadiol and its congeners. Furthermore, synthetic strategies are now readily envisioned toward other members of this class of terpenes by employing the versatile bicyclic β-lactone **9**, which can be readily prepared on a multigram scale.

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[22] CCDC 830937 (**19**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

