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Synthesis of (+)-Omphadiol and (+)-Pyxidatol C

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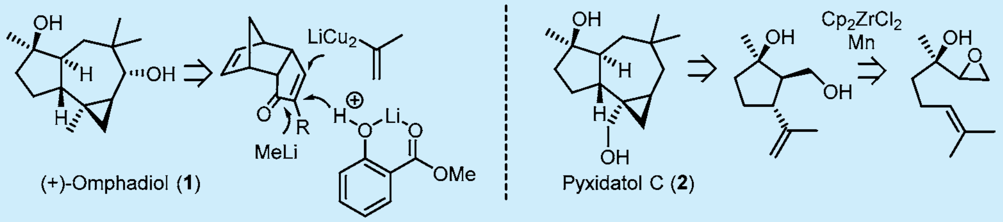
Supporting Information



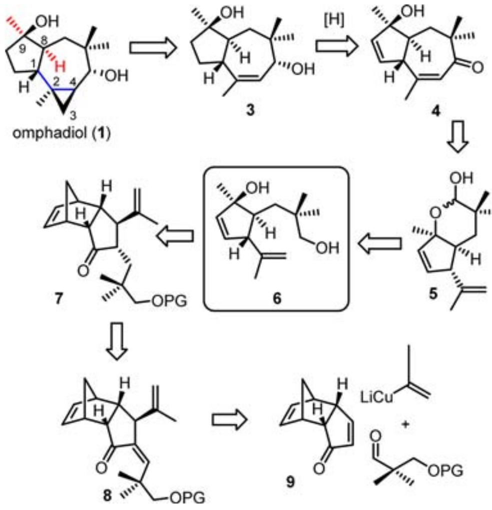
ABSTRACT: The synthesis of (+)-omphadiol and (+)-pyxidatol C was achieved through two independent strategies. For the synthesis of (+)-omphadiol, dicyclopentadienone was used as the workbench on which the three contiguous stereocenters of the cyclopentane could be introduced selectively. These include a tertiary alcohol and a selective protonation of an enolate. A ring-closing metathesis and a cyclopropanation concluded the synthesis. For the synthesis of pyxidatol C, we used the epoxide derived from (*R*)-linalool that was transformed to cyclopentane **23**. After chain extension, another ring-closing metathesis followed by oxidation state changes and finally a cyclopropanation led to (+)-pyxidatol C.

(+)-Omphadiol (**1**) is a sesquiterpene isolated[1] from the culture broth of *Omphalotus illudosin* by McMorris et al. in 2000. This basidomycete is a rich source of various sesquiterpenes, most of which were found to possess antibacterial properties. However, (+)-omphadiol was not tested for biological activities due to its scarcity from natural sources. The structure of (+)-omphadiol was elucidated with the aid of X-ray crystallography and high-field NMR experiments. (+)-Omphadiol contains six contiguous stereogenic centers embedded in a 5−7−3-fused tricyclic skeleton. In view of its scarcity and inspired by its challenging structure, we started a synthesis program that aimed at providing access to this natural product.

The first total synthesis of (+)-omphadiol was reported by Romo and co-workers[2] in 12 steps and 18% overall yield. Their synthesis involved introduction of the six contiguous stereogenic centers by substrate-controlled operations from (*R*)-carvone without using protecting groups. Recently, a racemic total synthesis of omphadiol and pyxidatol C from a common intermediate was reported by Liang and co-workers,[3] who utilized a stereospecific Tiffeneau−Demjanov rearrangement and an aldol−Henry cascade to prepare the *trans*-decalin core present in both natural products.

The major challenge in (+)-omphadiol's synthesis was the introduction of the contiguous stereocenters at C1, C8, and C9 of the cyclopentane subunit. To control the stereoselective construction of these centers, we took advantage of the tricyclopentane framework of norbornene derivative **9**, which directed addition of nucleophiles and protons to the convex face of the substrate. Retrosynthetically, (+)-omphadiol can be constructed from advanced intermediate **3** through a stereoselective cyclopropanation of the C2−C4 double bond (Scheme 1). Compound **3** would be generated from intermediate **4** by selective reduction of one double bond and stereoselective reduction of the keto carbonyl group.

Scheme 1. Retrosynthetic Disconnection of (+)-Omphadiol



The seven-membered ring of compound **4** could be constructed via a ring-closing metathesis (RCM) of a triene resulting from addition of vinyl Grignard onto lactol **5**, which could, in turn, be synthesized from diol **6** by partial oxidation. The 3° hydroxyl group of compound **6** could be introduced by a stereoselective nucleophilic addition of an appropriate Grignard

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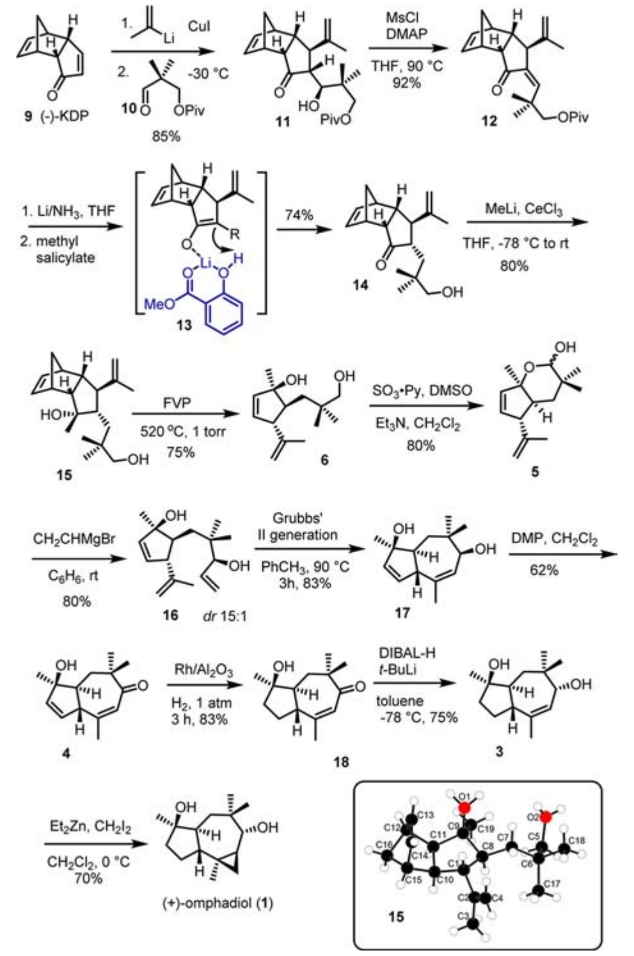
reagent to ketone **7** followed by subsequent flash vacuum pyrolysis (FVP, 4 + 2 cycloreversion).[4] Ketone **7** could be synthesized from enone **8** via reduction of the enone followed by stereoselective protonation of the resulting enolate. Enone **8** then could be derived from the known optically pure ketone **9**[5] through a 1,4-addition followed by aldol condensation.

Thus, our synthesis of (+)-omphadiol began with the sequence of 1,4-addition followed by aldol reaction with aldehyde **10** to provide aldol product **11** as a single diastereomer (Scheme 2).[6]

Scheme 2. Synthesis of (+)-Omphadiol



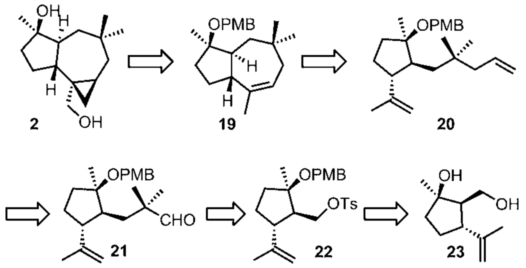
The observed selectivity during the 1,4-addition step took advantage of the convex structure of the substrate. Subsequent elimination afforded enone **12** in excellent yield, which was reduced under dissolving metal conditions (Li/NH_3) to generate its corresponding enolate and was subjected to face-selective protonation using methyl salicylate.[7] Under these conditions, concomitant deprotection of the pivalate took place together with small amounts of rehydration to compound **11**. Next, ketone **14** was further subjected to an *exo*-selective facial methyl addition mediated by $CeCl_3$ to give the desired diol **15**. Its stereochemistry was further confirmed by X-ray analysis.[8] The retro-Diels−Alder reaction of **15** under FVP[4] afforded diol **6** without any stereochemical scrambling. Partial oxidation of diol **6** utilizing the Parikh−Doering oxidation[9] afforded lactol **5**, which upon vinyl Grignard addition gave triene **16** in a 15:1 selectivity, which presumably reflects the chelation of the alkoxide to the aldehyde. The key RCM reaction of triene **16** gave the desired bicyclic core **17** in excellent yield, and the resulting allylic alcohol was oxidized[10] to the corresponding enone **4** in moderate yields. The chemoselective reduction of the olefin in the presence of enone was achieved with Rh/Al_2O_3 hydrogenation[11] to give enone **18**. The stereoselective reduction of the resulting enone took advantage of the bicyclic framework of compound **18** and the sterically hindered reducing agent generated from DIBAL-H and *t*BuLi. Finally, a non-hydroxyl-directed cyclopropanation completed the total synthesis of (+)-omphadiol.

Pyxidatol C (**2**), a sesquiterpediol isolated[1b] from *Clavicorona pyxidata*, has been used in traditional Chinese medicine for gastric pain, dyspepsia, gout, and heat toxicity. It is structurally related to (+)-omphadiol (**1**) and exhibits only a different oxidation pattern of the otherwise identical carbon skeleton. As in (+)-omphadiol, the four contiguous stereogenic centers are located at the juncture of the tricyclic skeleton, making it a challenging synthetic target. To date, only one racemic total synthesis has been reported.[3]

When we carried out the pyxidatol C synthesis in an analogous way compared to the (+)-omphadiol synthesis by utilizing the common intermediate **5**, we encountered significant problems.[12] Due to these problems, we devised an alternative strategy.

We envisioned that the introduction of the hydroxyl group at C12 could be achieved by a SeO_2-mediated allylic oxidation of compound **19** followed by a cyclopropanation (Scheme 3). The bicyclic compound **19**, in turn, could be obtained from the diene **20** by RCM, which could be synthesized from the aldehyde **21** by homologation followed by Wittig olefination. Aldehye **21** could be obtained by alkylation of isobutyronitrile with compound **22**. The tosylate **22** could be derived from the known diol **23**, which could be prepared from (−)-linalool by epoxide radical cyclization.[13]

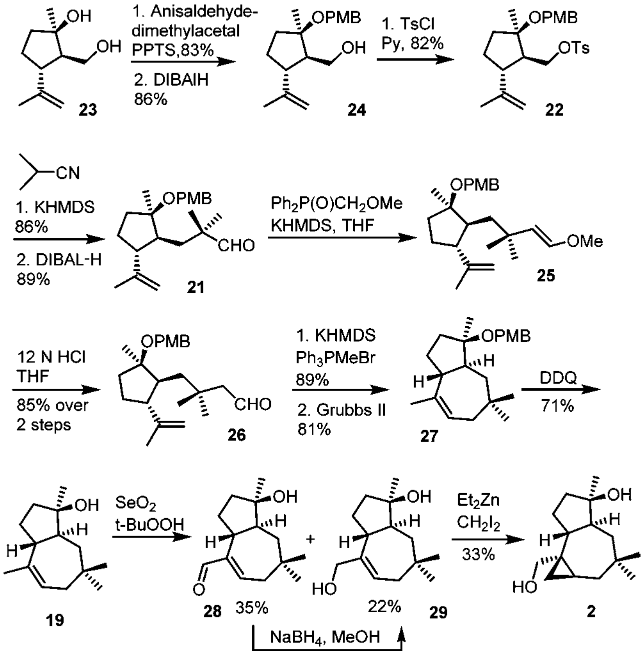
Scheme 3. Retrosynthetic Disconnection of Pyxidatol C



Accordingly, we began our synthesis with protection of the tertiary alcohol as PMB ether **24** by regioselective reduction of the previously generated acetal (Scheme 4).[14] The so-liberated primary hydroxyl group was converted into tosylate **22** and used in an alkylation with isobutyronitrile and KHMDS. Partial reduction of the so-generated nitrile with DIBAL-H generated aldehyde **21**, which was further subjected for homologation by a Horner−Wittig reaction to establish enol ether **25**.[15] Hydrolysis of **25** in a two-phase system with aqueous HCl in THF provided the extended aldehyde **26** in 89% yield over two steps.

This aldehyde was transformed to the corresponding olefin (89%) and subjected to a RCM reaction using the Grubbs' second-generation catalyst. After removal of the PMB group, oxidation with SeO_2[16] generated the desired alcohol **29** along with *α*,*β*-unsaturated aldehyde **28** (51%). The latter could be converted to alcohol **29** with $NaBH_4$ quantitatively. Finally, the face-selective cyclopropanation of allylic alcohol **29** under Simmons−Smith conditions[17] gave (+)-pyxidatol C. The

Scheme 4. Synthesis of Pyxidatol C



spectroscopic data of synthetic (+)-pyxidatol C were in good accordance with those of the authentic natural product.[18] Even though the authors did not determine the absolute configuration in their isolation paper, the close absolute value for the optical rotation and the identical sign of both compounds are strong indications that the enantiomer reported herein is identical to the authentic material.

In summary, we used the rigid conformation of the bicyclic ring system to control three out of the four chiral centers in (+)-omphadiol. A flash vacuum pyrolysis then liberated the carbon skeleton of (+)-omphadiol. The cyclopropanation and carbonyl reduction were performed diastereoselectively and completed the synthesis of (+)-omphadiol with minimum use of protecting groups.

Even though (+)-omphadiol and (+)-pyxidatol C differ only in their oxygenation pattern, the strategy that worked for (+)-omphadiol was not applicable for (+)-pyxidatol. However, an alternative approach using an epoxide radical cyclization to generate compound **23** could be successfully applied to the total synthesis of this natural product.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00814.

Experimental procedures and spectral data of compounds described herein (PDF)
X-ray data for **15** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) McMorris, T. C.; Lira, R.; Gantzel, P. K.; Kelner, M. J.; Dawe, R. *J. Nat. Prod.* **2000**, *63*, 1557. (b) Zheng, Y.-B.; Lu, C.-H.; Zheng, Z.-H.; Lin, X.-H.; Su, W.–J.; Shen, Y. – M. *Helv. Chim. Acta* **2008**, *91*, 2174.

(2) Liu, G.; Romo, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 7537.

(3) Zhou, L.; Yao, Y.; Xu, W.; Liang, G. *J. Org. Chem.* **2014**, *79*, 5345.

(4) (a) McNab, H. *Contemp. Org. Synth.* **1996**, *3*, 373. (b) Donohoe, T. J.; Johnson, P. D.; Pye, R. J.; Keenan, M. *Org. Lett.* **2005**, *7*, 1275. (c) Klunder, A. J. H.; Zhu, J.; Zwanenburg, B. *Chem. Rev.* **1999**, *99*, 1163.

(5) (a) Shao, C.; Yu, H.–J.; Wu, N.–Y.; Feng, C.–G.; Lin, G.–Q. *Org. Lett.* **2010**, *12*, 3820. (b) Tanaka, K.; Ogasawara, K. *Synthesis* **1995**, *1995*, 1237. (c) Hiroya, K.; Zhang, H. L.; Ogasawara, K. *Synlett* **1999**, *1999*, 529. (d) Takano, S.; Inomata, K.; Ogasawara, K. J. *J. Chem. Soc., Chem. Commun.* **1989**, 271.

(6) Snider, B. B.; Yang, K. *J. Org. Chem.* **1992**, *57*, 3615.

(7) (a) Kleinman, E.; Heathcock, C. H. *Tetrahedron Lett.* **1979**, *20*, 4125. (b) Heathcock, C. H.; Kleinman, E. F.; Binkley, E. S. *J. Am. Chem. Soc.* **1982**, *104*, 1054. (c) Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1984**, *25*, 1599. (d) Krause, N. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1764.

(8) The crystal structure was deposited at the Cambridge Crystallographic Data Centre. Deposition number CCDC 1461679.

(9) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(10) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(11) Furber, M.; Mander, L. N.; Patrick, G. L. *J. Org. Chem.* **1990**, *55*, 4860.

(12) This will be discussed in a following full paper.

(13) (a) Morales, C. P.; Catalán, J.; Domingo, V.; González Delgado, J. A.; Dobado, J. A.; Herrador, M. M.; Quílez del Moral, J. F.; Barrero, A. F. *J. Org. Chem.* **2011**, *76*, 2494. (b) Langhanki, J.; Rudolph, K.; Erkel, G.; Opatz, T. *Org. Biomol. Chem.* **2014**, *12*, 9707.

(14) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593.

(15) Earnshaw, C.; Wallis, C. J.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, *12*, 3099.

(16) (a) Stephenson, L. M.; Speth, D. R. *J. Org. Chem.* **1979**, *44*, 4683. (b) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526. (c) Rapoport, H.; Bhalerao, U. T. *J. Am. Chem. Soc.* **1971**, *93*, 4835. (d) Hoekstra, W. J. In *e-EROS Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, UK, 1995; Vol. 6, p 4437.

(17) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256. (b) Lou, J.; Hashimoto, M.; Berova, N.; Nakanishi, K. *Org. Lett.* **1999**, *1*, 51. (c) Poulter, C. D.; Friedrich, E. C.; Winstein, S. *J. Am. Chem. Soc.* **1969**, *91*, 6892.

(18) See the Supporting Information for comparison of analytical data.