Communication

A Highly Convergent and Biomimetic Total Synthesis of Portentol

Bichu Cheng, and Dirk Trauner

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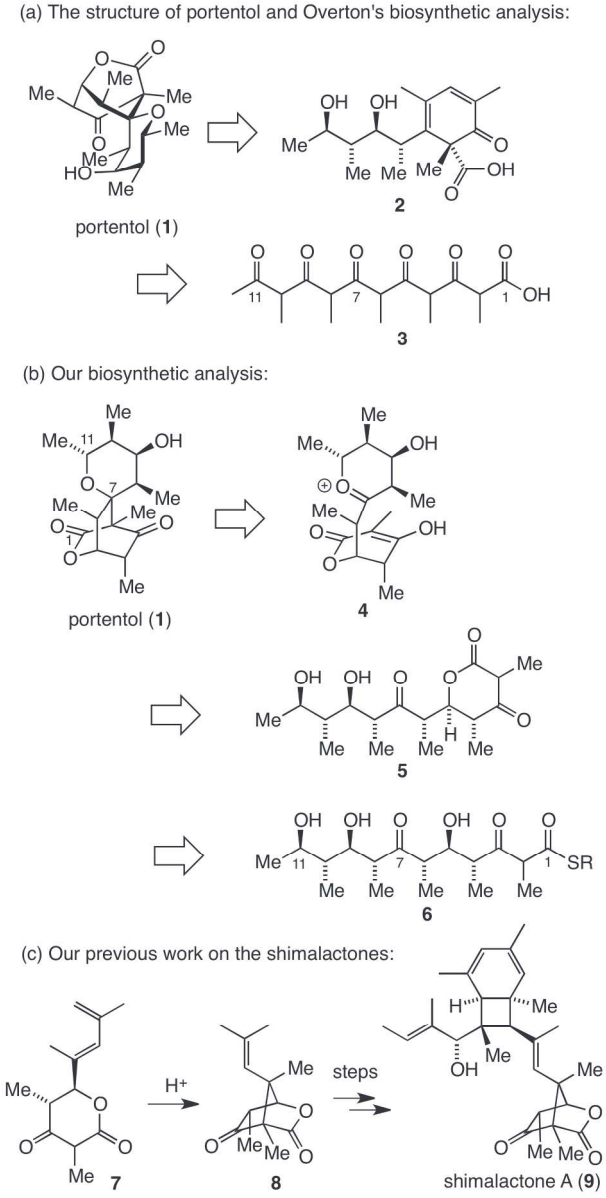

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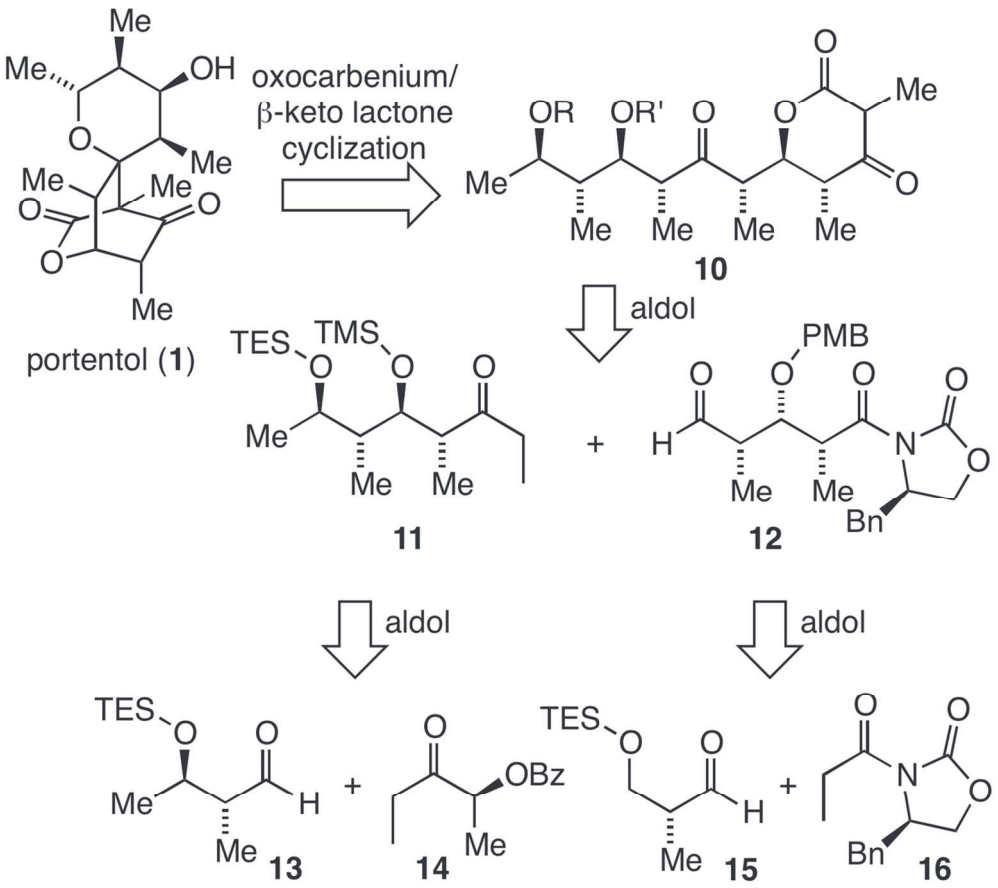

Retrosynthesis of Portentol
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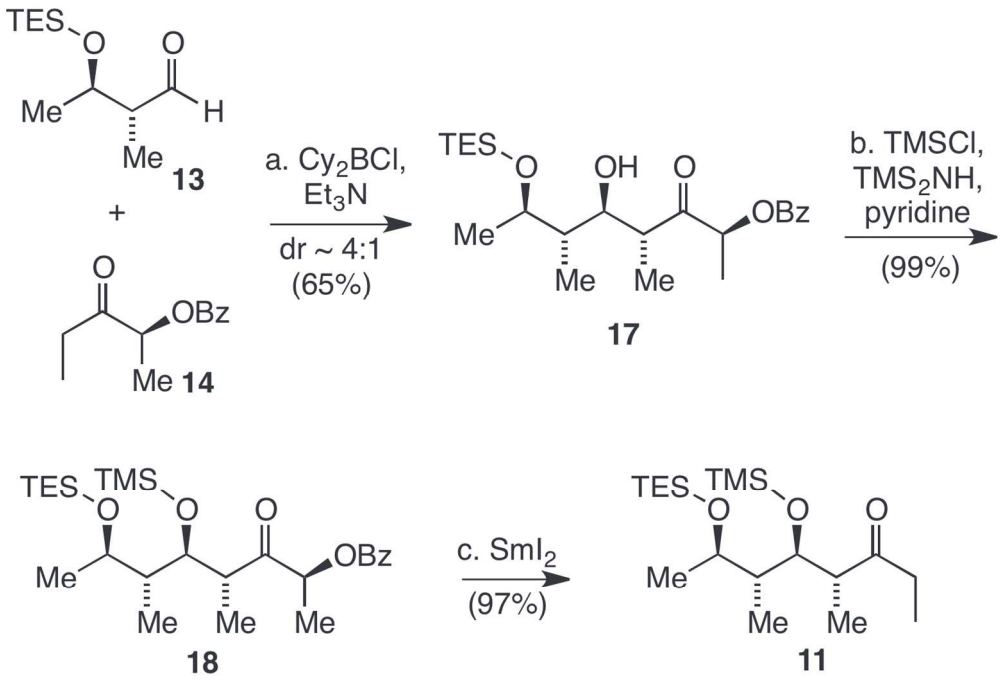

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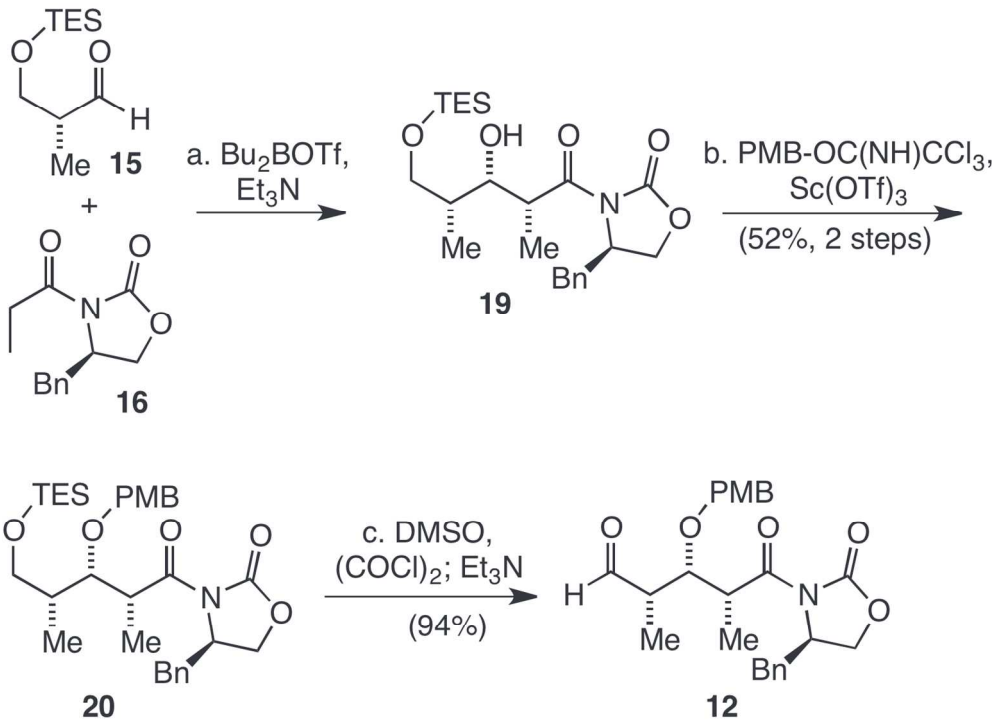

Synthesis of Aldehyde Fragment 12
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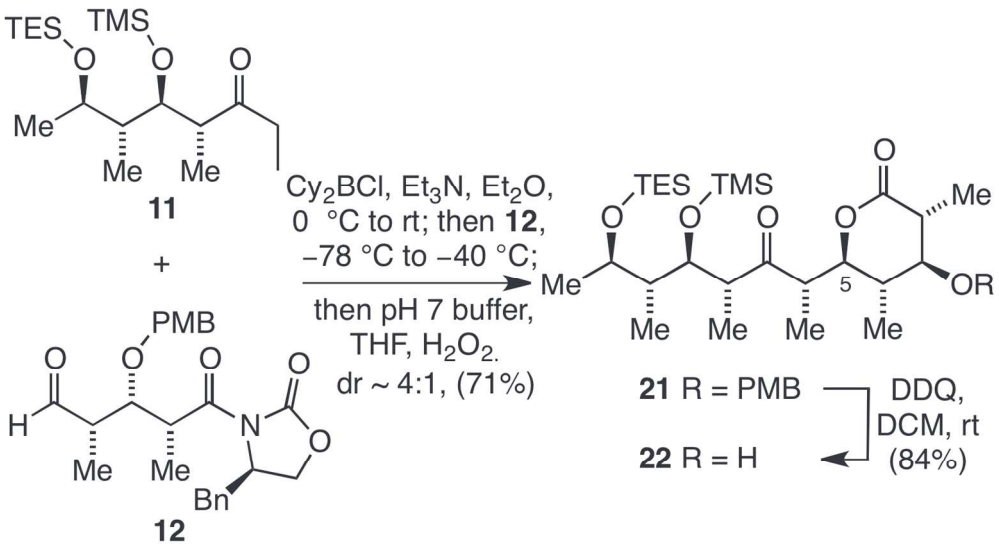

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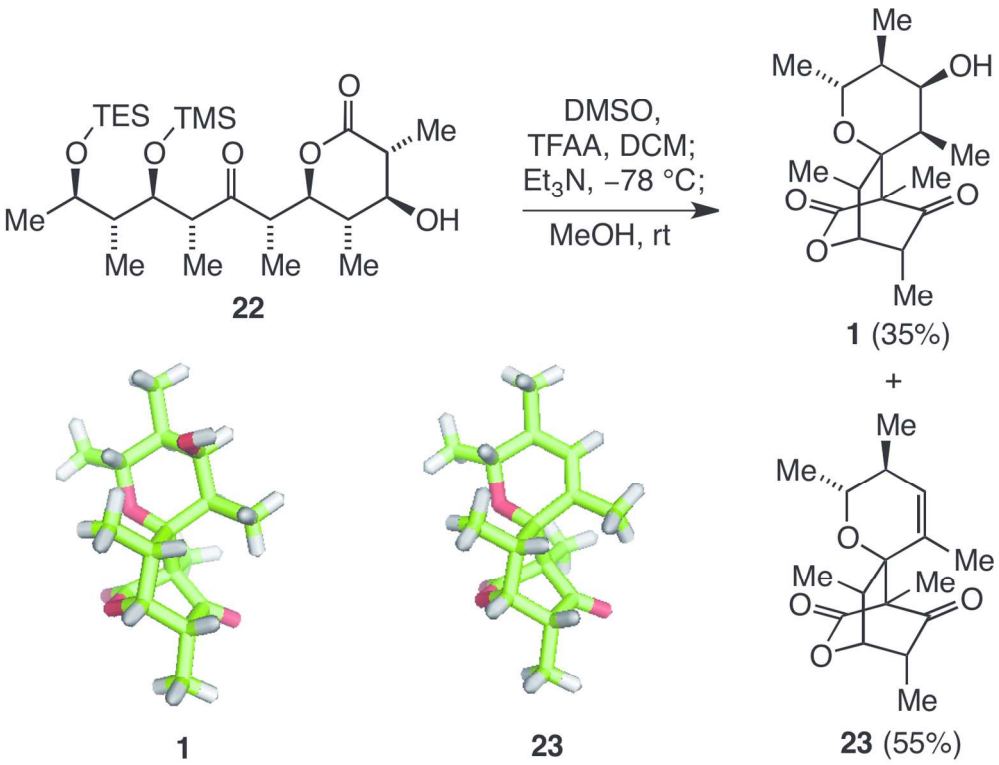

Total Synthesis of Portentol and Anhydroportentol
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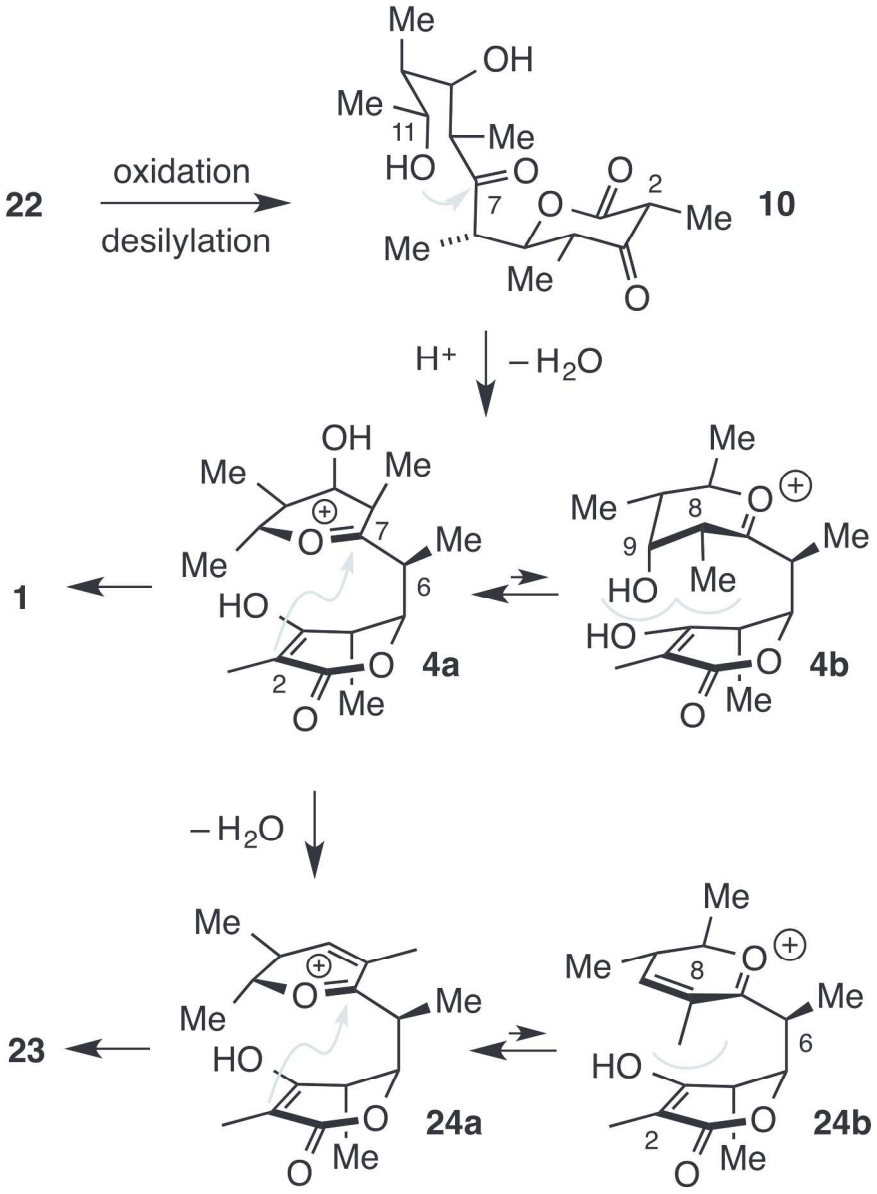

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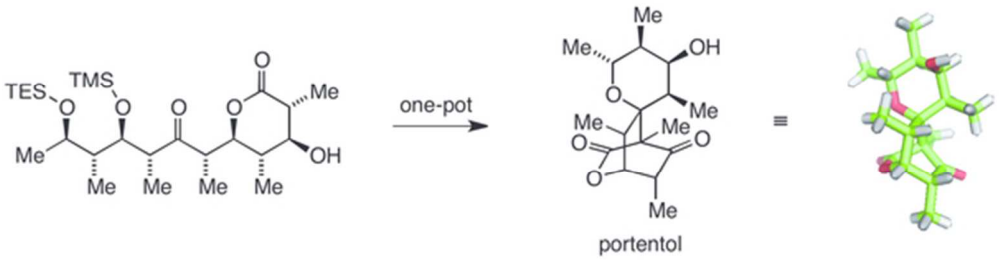

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A Highly Convergent and Biomimetic Total Synthesis of Portentol

Bichu Cheng, Dirk Trauner*

Department of Chemistry and Center for Integrated Protein Science, Ludwig-Maximilians-Universität München, Butenandtstrasse 5-13, 81377 München Germany

Supporting Information Placeholder

ABSTRACT: An efficient total synthesis of the unusual polyketide portentol is reported. Three boron aldol reactions were used to assemble the linear carbon chain of the natural product, which contains two challenging *anti*, *anti*-stereotriads. A biomimetic double cyclization cascade, triggered by an oxidation, then afforded portentol and its known dehydration product, anhydroportentol. The biosynthesis of portentol and the biosynthetic relevance of our key step are discussed.

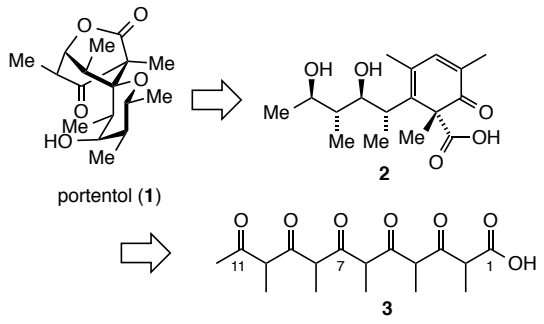
Portentol (**1**) is a complex polyketide that is unusual in several respects. It was first isolated in 1967 from the lichen *Roccella portentosa* and subsequently found in a variety of other lichens and in extracts from the Brazilian nut tree *Gustavia hexapetala*.[1] Biological testing showed moderate growth inhibition activity against several cancer cell lines.[1j] The molecule has a unique and complex structure, which after detailed NMR investigations and degradation studies was ultimately secured by single crystal X-ray analysis. Its densely functionalized *spiro* tricyclic core features nine consecutive stereocenters, including two adjacent tetrasubstituted ones, which renders portentol a challenging target for total synthesis. To the best of our knowledge, however, the synthesis of portentol or a comparable polyketide has not been reported to date.[2]

Biosynthetically, it has been proposed that portentol is formed from linear polyketide **3** via cyclohexadienone intermediate **2** (Scheme 1a).[1g] Isotope-labeling studies showed that acetate and malonate were incorporated into the carbon chain of portentol. While the terminal secondary methyl group originates from the C2 of acetate, the remaining five methyl groups are shown to come from methionine.[3]

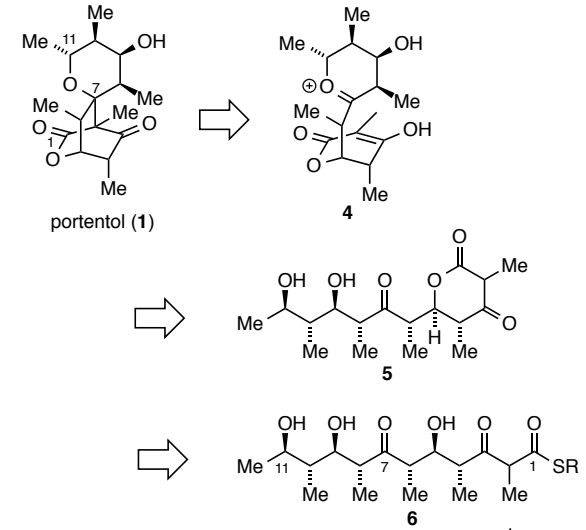
Here, we report our own biosynthetic speculations and synthetic efforts toward this natural product, which have enabled a short, highly convergent, and stereoselective total synthesis of portentol.

Scheme 1. Biosynthetic Speculations

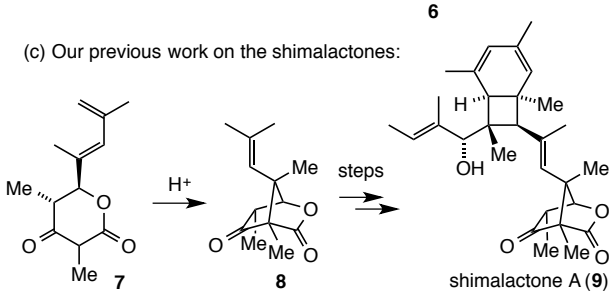
(a) The structure of portentol and Overton's biosynthetic analysis:



(b) Our biosynthetic analysis:



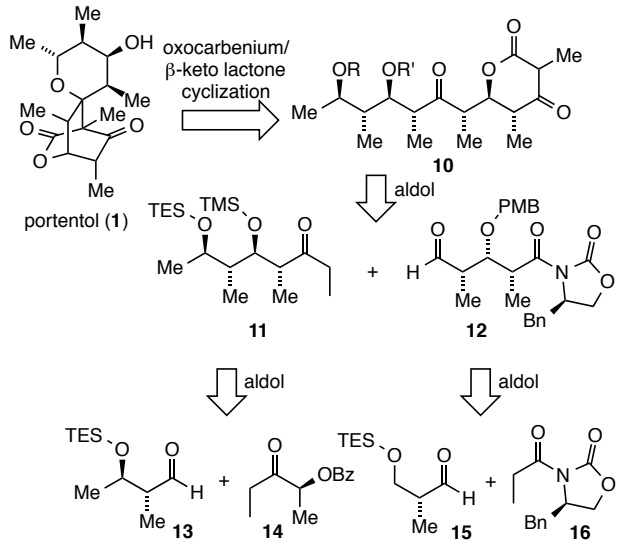
(c) Our previous work on the shimalactones:



We propose that portentol is formed *via* a cationic cyclization cascade (Scheme 1b). The last bond formation would involve the intramolecular nucleophilic addition of an enolized β-keto-δ-lactone moiety onto a cyclic oxocarbenium ion in intermediate **4**.[4] This intermediate, in turn, would stem from precursor **5** via nucleophilic attack of the hydroxy group at C11 onto the C7 carbonyl, followed by protonation and loss of water. Precursor lactone **5** would be assembled by a type II polyketide synthetase (PKS) via the fully linear enzyme-bound thioester **6**. It is conceivable that the thioesterase domain of the PKS not only catalyzes the β-keto-δ-lactone formation but also the subsequent cationic cyclization to yield portentol. Analogous chemistry was used in our biomimetic synthesis of shimalactone A (Scheme 1c). It involved the cyclization of β-keto-δ-lactone **7**, triggered by a protonation of its diene moiety, to yield oxabicyclo[2.2.1]heptane **8**.[5]

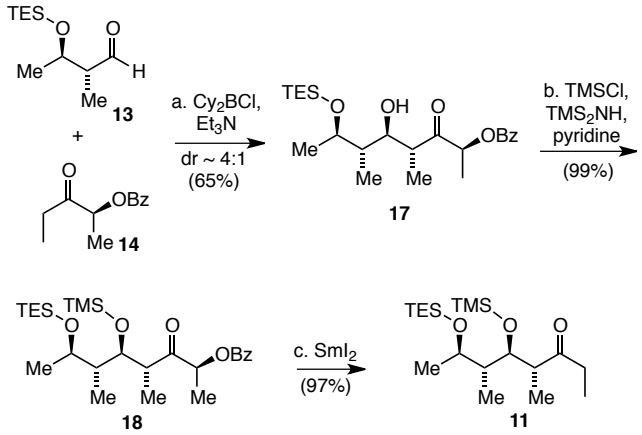
Our synthetic strategy towards portentol aimed to mimic our proposed biosynthesis (Scheme 2). We envisioned that the spirocyclic core of the natural product could be formed by an intramolecular double cyclization cascade starting from β-keto-δ-lactone **10**. This compound is a masked form of intermediate **5** in our proposed biosynthesis and contains two *anti-anti* stereotriads.[6] Triads of this type are a challenge, even after decades of progress in acyclic stereoselection.[6] We envisioned that **10** could be synthesized by an *anti* aldol reaction of "left hand" ketone **11** and "right hand" aldehyde **12**, two fragments of similar size and complexity. These compounds, in turn, would be assembled using two aldol reactions that would involve known ketones and aldehydes.

Scheme 2. Retrosynthesis of Portentol.



Accordingly, our synthesis of ketone **11** started from aldehyde **13**[7] and ketone **14**[8]. Both were made in two steps using slightly modified literature procedures (*supporting information*). Paterson aldol reaction of aldehyde **13** and ketone **14** then afforded the corresponding aldol adducts with a 4:1 dr favoring the desired *anti* diastereomer **17**.[9] It could be isolated by flash column chromatography in 65% yield. Single crystal X-ray analysis of a derivative confirmed the assigned configuration (*supporting information*).

Scheme 3. Synthesis of Ketone Fragment **11**.

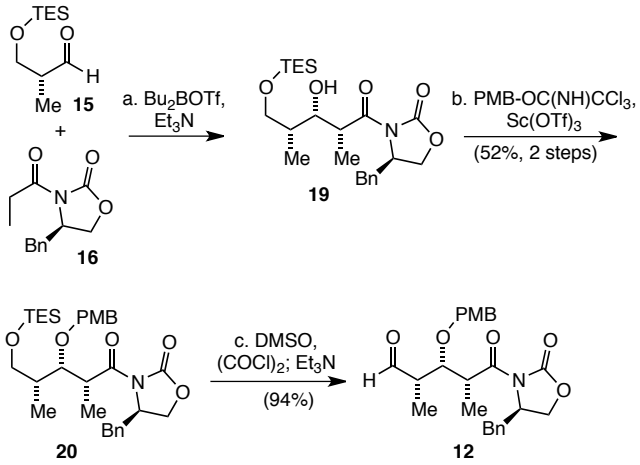


Reagents and conditions: (a) Cy_2BCl, Et_3N, Et_2O, –78 °C to 0 °C, then **13**, –78 °C to –20 °C, 65% (4:1 dr); (b) TMSCl, TMS_2NH, pyridine, rt, 99%; (c) SmI_2, THF/MeOH, 0 °C, 97%.

Next, we protected the secondary alcohol of **17**. Reaction of **17** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and triethylsilyl trifluoromethanesulfonate (TESOTf) afforded the corresponding silyl ethers cleanly, but it was later ascertained that these groups were difficult to remove at the final stage of the synthesis. We then decided to protect the alcohol as the trimethylsilyl (TMS) ether. After screening several conditions, TMS ether **18** was prepared in quantitative yield using hexamethyldisilazane (TMS_2NH) and TMSCl in pyridine.[10] Reductive removal of the α-benzoate with SmI_2 then afforded the "left hand" ketone **11** in good yield (Scheme 3).[11]

The synthesis of "right-hand"-aldehyde **12** began with an Evans *syn* aldol reaction[12] of known aldehyde **15**, derived from the (*R*)-Roche ester, with oxazolidinone **16**.[13] The resulting aldol product **19** was protected as *p*-methoxybenzyl (PMB) ether **20**,[14] and the protected primary alcohol was desilylated and oxidized under Swern condition to give aldehyde **12** (Scheme 4).[15]

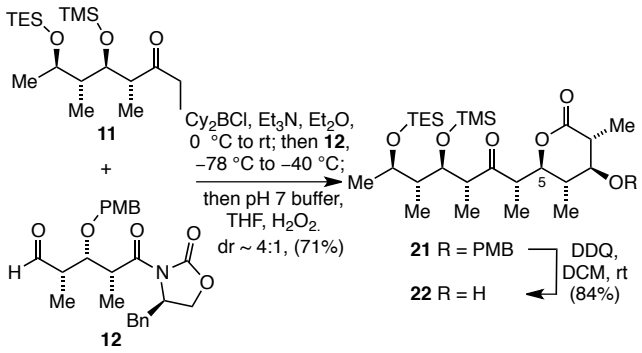
Scheme 4. Synthesis of Aldehyde Fragment **12**.



Reagents and conditions: (a) Bu_2BOTf, Et_3N, DCM, 0 °C, then **15**, –78 °C to 0 °C; (b) PMB-OC(NH)CCl_3, $Sc(OTf)_3$ (1 mol%), toluene, rt, 52% (2 steps, unoptimised); (c) DMSO, $(COCl)_2$, DCM, –78 °C to –25 °C; Et_3N, 94%.

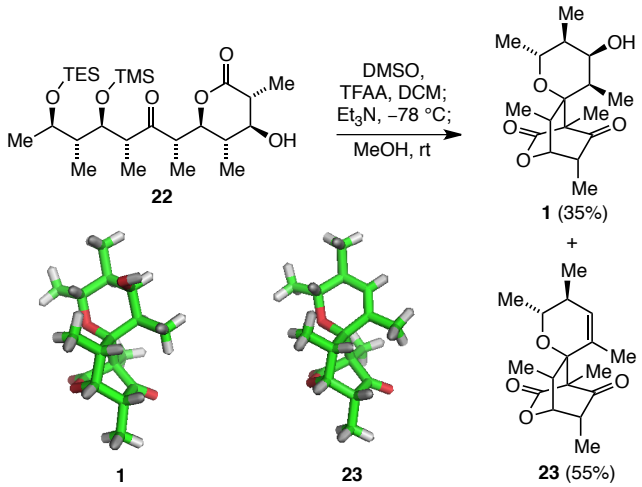
With both fragments **11** and **12** in hand, we started to investigate the key coupling reaction. The union of the two fragments followed a procedure reported by Evans with slight modification.[16] Stirring ketone **11** with Cy_2BCl and Et_3N in diethyl ether for 1 hour at 0 °C and 2 hours at room temperature gave a boron enolate, which was added to a suspension of aldehyde **12** in diethyl ether at –78 °C. The reaction mixture was then stirred at –40 °C for 1–2 days until no aldehyde **12** remained, as determined by thin layer chromatography (TLC) analysis. Although the aldol product could be isolated, it was found that the desired lactonization occurred spontaneously if THF was added as a cosolvent during the workup. Separation by flash column chromatography gave analytically pure lactone **21** and recovered starting material **11**. A ^1H NMR study of the H-H coupling constant ($^3J_{H\text{-}H}$) on the lactone ring suggested that the desired stereochemistry was obtained at C5. Next, the PMB group was oxidatively cleaved with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dichloromethane (DCM) to generate alcohol **22**. Adding water or pH 7 phosphate buffer to the reaction lead to byproduct formation, presumably due to the loss of silyl groups under these conditions (Scheme 5).

Scheme 5. Fragment Coupling.



With the full carbon chain successfully assembled, we began to investigate the double cyclization cascade to complete the synthesis of portentol. After extensive screening, oxidation of the β-hydroxy lactone could be achieved under Swern condition with trifluoroacetic anhydride (TFAA) as the activator.[17] Once the oxidation was complete, methanol was added to quench the reaction. To our delight, TLC and ^1H NMR analysis of the crude reaction mixture showed that both portentol (**1**) and the known derivative anhydroportentol (**23**)[1g] were formed cleanly in a 0.7:1 ratio. These two compounds were readily separated by flash column chromatography (silica gel). Portentol was thus isolated in 35% yield, and anhydroportentol was isolated in 55% yield. Their spectroscopic data were in accord with literature values,[1g, 1j] and single crystal X-ray structures of both compounds confirmed our assignment (Scheme 6).

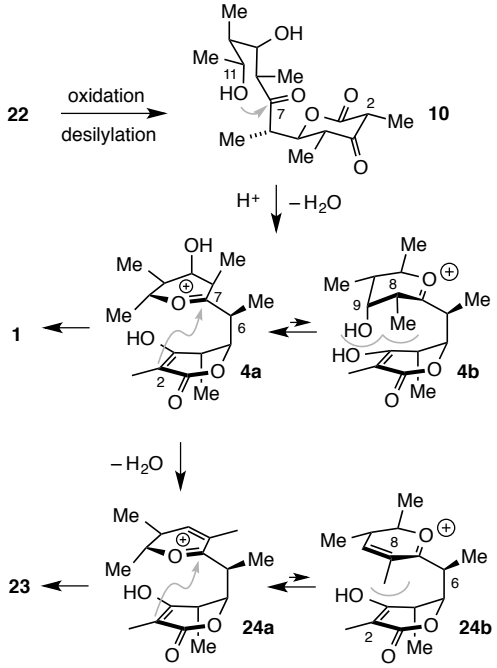
Scheme 6. Total Synthesis of Portentol and Anhydroportentol.



The proposed mechanism of this cascade is shown in Scheme 7. Oxidation of alcohol **22** presumably gave the corresponding β-keto lactone **10** in equilibrium with its enol form. The acid generated *in situ* during the workup removed the silyl protecting groups and induced the formation of oxocarbenium

4, which is shown here as a mixture of two conformers. One of them, 4a, undergoes C2-C7 cyclization to yield portentol (1). Rotation along the C6-C7 bond yields 4b, which cannot undergo cyclization fast enough due to a steric clash of the C8 methyl group and C9 hydroxy group with the C2 methyl group, which is apparent in molecular models. Due to steric hindrance, the formation of the C2-C7 bond is presumably a relatively slow process. Therefore, proton transfer in 4, followed by elimination of water can compete in the cascade, which yields the unsaturated oxocarbenium ion 24, again as a mixture of rotamers. Among these, 24a undergoes cyclization to afford anhydroportentol (23). Its rotamer 24b suffers from a steric clash between the C2 and C8 methyl groups and an unfavorable $A^{1,3}$-strain between the C6 and C8 methyl groups, which prevents rapid cyclization. Therefore, stereoisomers of portentol (1) and anhydroportentol (23) with respect to C7 are not observed. Given the high yield and ease of this cyclization process, we believe that a similar transformation occurs in Nature (as we proposed in Scheme 1b). Whether this happens spontaneously or requires enzymatic catalysis remains to be determined. The fact that anhydroportentol is easily formed but has not yet been isolated as a natural product points to the latter.

Scheme 7. Proposed Mechanism of the Double Cyclization Cascade.



In conclusion, we have achieved a total synthesis of portentol that owes its brevity and efficiency to a biomimetic key step and the convergent nature of our synthetic plan. Three diastereoselective boron aldol reactions, including one *syn* aldol reaction and two *anti* aldol reactions, were used to assemble the linear carbon chain. A double cyclization cascade formed the spirocyclic core and afforded portentol. Thus, this unusual and attractive natural product has finally yielded to total synthesis.

ASSOCIATED CONTENT

Supporting Information.

Experimental procedures and compound characterization data, ^{1}H, ^{13}C NMR spectra of new synthetic compounds and cif files for X-ray structures. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

dirk.trauner@lmu.de

Notes

The authors declare no competing financial interest.

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We thank SFB 749 (Dynamics and Intermediates of Molecular Transformations) for financial support, and Dr. Peter Mayer (LMU Munich) for X-ray structure determination. We also thank Mr. James Frank and Mr. Benjamin Williams for helpful discussions during the preparation of this manuscript.

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