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Natural Products Synthesis

Total Synthesis of the Tetracyclic Sesquiterpene (±)-Punctaporonin C**

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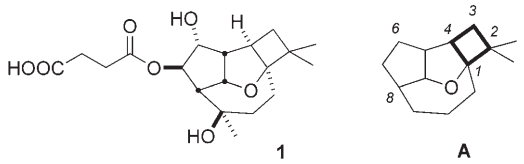
Dedicated to Professor Manfred T. Reetz on the occasion of his 65th birthday

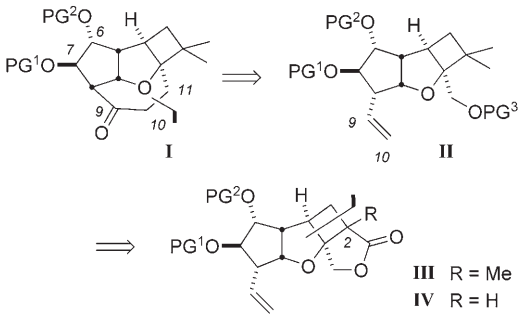
Punctaporonin C (**1**)[1] is a caryophyllene-related sesquiterpene which was isolated together with several structurally similar compounds, the punctaporonins,[1,2] from *Poronia punctata* (Linnaeus: Fries). The most complex representative of this compound class, punctaporonin C exhibits the unusual oxatetracyclo[6.3.2.0^{1,4}.0^{5,13}]tridecane skeleton **A** (Scheme 1).



Scheme 1. Structure of punctaporonin C (**1**) and its core skeleton **A** with the cyclobutane ring highlighted.

Although a hypothesis on the biosynthesis of the punctaporonins has been put forward,[1b] and the bi- and tricyclic punctaporonins A, B, and D have been accessed synthetically,[3] a total synthesis of punctaporonin C has not yet been reported. An intrinsic problem is the annulation of the four-membered ring to the highly substituted tetrahydrofuran moiety. An intermolecular [2+2] photocycloaddition[4] with simultaneous formation of the C1–C2 and C3–C4 bonds is impossible, as neither of the two potential reaction partners can display a suitable chromophore. For related, carbanalogous scaffolds, for example, the tricyclo[6.2.0.0^{2,6}]decane scaffold of kelsoene,[5] the intermolecular [2+2] photocycloaddition is feasible, as an enone serves as the chromophore. Herein, we report the first total synthesis[6] of racemic (±)-punctaporonin C, as well as a photochemical route to skeleton **A** by a selective intramolecular [2+2] photocycloaddition of a tetronate[7] and subsequent aldol ring closure.

Retrosynthetically (Scheme 2), punctaporonin C (**1**) was traced back to ketone **I**, in which the two hydroxy groups at C6 and C7 were to be protected orthogonally (PG = protecting group), and in which the carbonyl group was to serve as a precursor for the tertiary alcohol at C9. An intramolecular enolate alkylation was planned for the ring closure to form the unusual bridged oxepane. These considerations led to compound **II** as a precursor, which was chosen to enable the construction of an acetyl group (C9, C10) by a Wacker oxidation.[8] The carbon skeleton of the tricyclic compound **II** could be formed from lactone **III**, if a complete reduction of the carboxylic carbon atom to a methyl group was taken in account. The other methyl group at C2 of punctaporonin C was to be introduced by the alkylation of lactone **IV** to give **III**.



Scheme 2. Retrosynthetic analysis of punctaporonin C (**1**).

Lactone **IV** could obviously be formed through an intramolecular [2+2] photocycloaddition, with the decisive question being whether and how the two terminal double bonds in a precursor molecule could be distinguished. In preliminary studies on the [2+2] photocycloaddition, no selectivity was observed when ether was used as the solvent, and the wrong regioisomer was formed preferentially in the presence of cyclodextrins.[9] However, we now discovered that 1,3-divinyl-2-cyclopentyltetronates with a polar substituent at the 4-position undergo the cycloaddition in protic solvents to give predominantly the desired regioisomer. Indeed, the product **3**, which was required for the planned synthesis, was obtained from substrate **2** with acceptable selectivity (75:25; Scheme 3). We presume that the acetoxy group becomes sterically demanding as a result of hydrogen bonding with the solvent[10] and resides in a pseudoequatorial position in the envelope **2′**. As a consequence, the tetronate group and one of the two terminal double bonds are ideally positioned for an intramolecular [2+2] photocycloaddition. The facial and simple diastereoselectivity of the photoreaction were perfect: A single diastereoisomer was obtained.

The starting material for the successful total synthesis of punctaporonin C (Scheme 4) was the known *meso* epoxide **4**[9]

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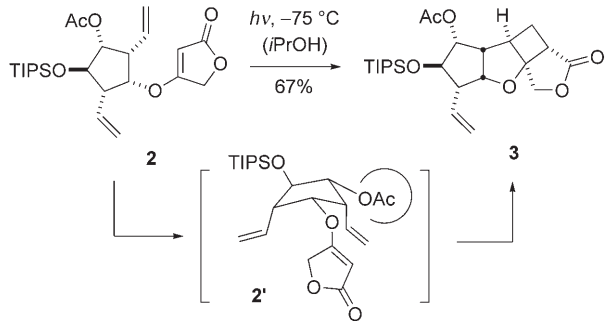
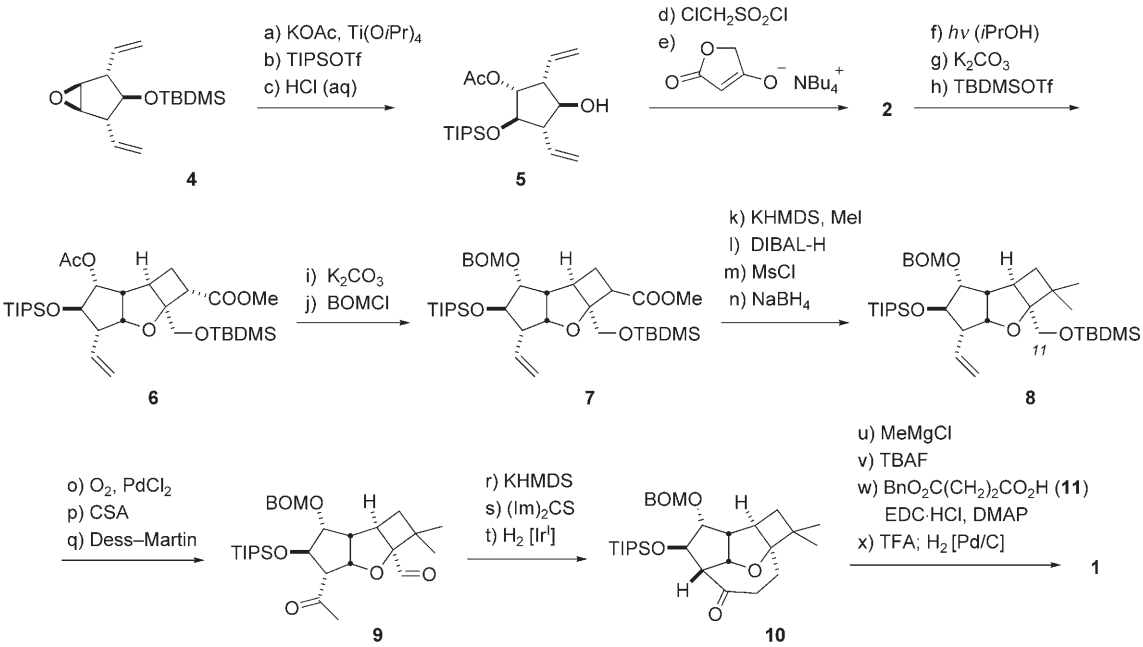


Scheme 3. Regio- and stereoselective [2+2] photocycloaddition of tetronate **2** to give **3**, with a depiction of the putative preferred conformation **2′**. Reaction conditions: *hν* ($\lambda = 254$ nm), *i*PrOH, −75 °C, 1.5 h, $c = 7$ mM.

(TBDMS = *tert*-butyldimethylsilyl). After epoxide opening[11] with KOAc, the free hydroxy group was protected as its triisopropylsilyl (TIPS) ether. Selective cleavage of the TBDMS ether led to alcohol **5**, which was converted into the tetronate **2** depicted in Scheme 3. The use of chloromethanesulfonate[12] as a leaving group was essential for the high-yielding formation of product **2** (80%) in the alkylation step, which proceeded with inversion of configuration. The best yield observed with the methanesulfonate was 30%; the trifluoromethanesulfonate was unstable.

After the intramolecular [2+2] photocycloaddition of **2**, the lactone was opened under mild conditions, and the free primary alcohol was protected as its TBDMS ether. As the acetyl group in the product **6** was not suitable as a protecting group in the planned alkylation, it was replaced by a benzyloxymethyl (BOM) group. Further transformations were carried out at the cyclobutane ring of the ester **7**. The introduction of a methyl group by enolate alkylation was followed by complete reduction of the exocyclic methoxycarbonyl group to a second methyl group.

The Wacker oxidation[8] of **8** proceeded smoothly and in excellent yield (94%), so that after deprotection of the primary alcohol and the installation of suitable leaving groups (methanesulfonate, iodide) at C11, the formation of the oxepane ring through an intramolecular enolate alkylation could be investigated. Unfortunately, all attempts to carry out this transformation failed, presumably because the leaving group can not align itself properly for an S_N2-type reaction as a result of the adjacent geminal dimethyl substitution. Oxidation[13] of the free alcohol to the aldehyde **9** finally enabled ring closure by an aldol reaction. After elimination[14] and chemoselective hydrogenation[15] of the double bond, the



Scheme 4. Total synthesis of (±)-punctaporonin C (**1**): a) KOAc, $Ti(OiPr)_4$ (50 mol%), HOAc, 90 °C, 9 h, 76%; b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 3 h; c) HCl (aq), MeOH, 20 °C, 6 h, 91% for 2 steps; d) chloromethanesulfonyl chloride, pyridine, −10 °C, 4 h, 95%; e) tetrabutylammonium tetronate, THF, 67 °C, 20 h, 80%; f) *hν*, *i*PrOH, −75 °C, 1.5 h, d.r. 75:25; g) K_2CO_3 (20 mol%), MeOH, −20 °C, 2 h; h) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, −20 °C, 3 h, 60% for 3 steps; i) K_2CO_3, MeOH, 20 °C, 3 days, 80%; j) BOMCl, TBAI, $NEtiPr_2$, $ClCH_2CH_2Cl$, 50 °C, 36 h, 80%; k) KHMDS, MeI, THF, −40→−78 °C, 3 h, d.r. 80:20, 56%; l) DIBAL-H, THF, −78 °C, 4 h, 81%; m) MsCl, NEt_3, CH_2Cl_2, −20 °C, 4 h, quantitative; n) $NaBH_4$, DMPU, 75 °C, 24 h, 77%; o) O_2, $PdCl_2$, CuCl, DMF/H_2O (10:1), 20 °C, 4 days, 94%; p) CSA (50 mol%), CH_2Cl_2/MeOH (10:1), 20 °C, 24 h, 91%; q) Dess–Martin, CH_2Cl_2, 20 °C, 1 h, quantitative; r) KHMDS, THF, −78→−40 °C, 30 min, 56%; s) $(Im)_2CS$, DMAP, CH_2Cl_2, 20→40 °C, 16 h, quantitative; t) H_2, $[Ir(cod)P(c\text{-}C_6H_{11})_3(py)]PF_6$ (10 mol%), CH_2Cl_2, 20 °C, 2 h, 94%; u) MeMgCl, Et_2O, 20 °C, 16 h, d.r. 87:13, 83%; v) TBAF, THF, 0 °C, 3 h, 89%; w) $BnO_2C(CH_2)_2CO_2H$ (**11**), EDC·HCl, DMAP, CH_2Cl_2, 20 °C, 16 h, 95%; x) TFA, CH_2Cl_2, 20 °C, 1.5 h; H_2, Pd/C, MeOH/ethyl acetate (1:1), 20 °C, 16 h, 85% for 2 steps. Bn = benzyl, BOMCl = benzyloxymethyl chloride, cod = 1,5-cyclooctadiene, CSA = camphorsulfonic acid, DIBAL-H = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, DMPU = 1,3-dimethyltetrahydropyrimidin-2(1*H*)-one, EDC = *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide, HMDS = hexamethyldisilazide, $(Im)_2CS$ = thiocarbonyldiimidazole, Ms = methanesulfonyl, py = pyridine, TBAF = tetrabutylammonium fluoride, TBAI = tetrabutylammonium iodide, Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid.

desired ketone **10** was obtained. Surprisingly, the Grignard addition of readily accessible MeMgI at low temperature (−10 °C) provided the wrong diastereoisomer (diastereomeric ratio (d.r.) 34:66), which resulted from a pseudoaxial attack. By changing the counterion and carrying out the reaction at room temperature, we obtained the desired tertiary alcohol with good diastereoselectivity (d.r. 87:13). The final three steps were unproblematic. The target molecule **1** was accessed by introducing the succinic acid side chain as its monoprotected derivative **11**. The originally planned parallel hydrogenolysis of the BOM protecting group and the benzyl ester was unsuccessful. It was therefore necessary to remove the BOM group first under acidic conditions,[16] and to cleave the benzyl ester subsequently by hydrogenolysis.

In summary, the synthesis of racemic (±)-punctaporonin C was completed successfully in 24 steps from epoxide **4** in an overall yield of 2.0%. Although the photochemical key step was performed early in the synthesis, the supply of material for the completion of the synthesis was never an issue. All scalar physical properties of the synthetic product were identical to those of the natural product.[1,17] We are currently investigating the biological activity of the product and evaluating the use of the scaffolds accessible by the photocycloaddition of tetronates in medicinal chemistry.[18]

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