Enantiocontrolled construction of sistodiolynne, an unusual polyketide from the wood-decay fungus *Sistrema raduloides*

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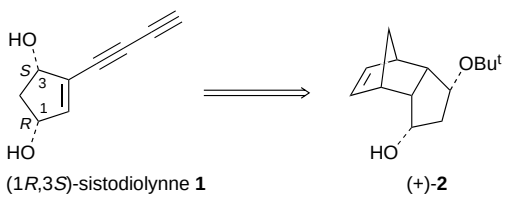
Sistodiolynne, an unusual polyketide isolated from the wood decay fungus *Sistorema raduloides*, has been constructed stereoselectively from a chiral cyclopentenol building block to verify the proposed structure.

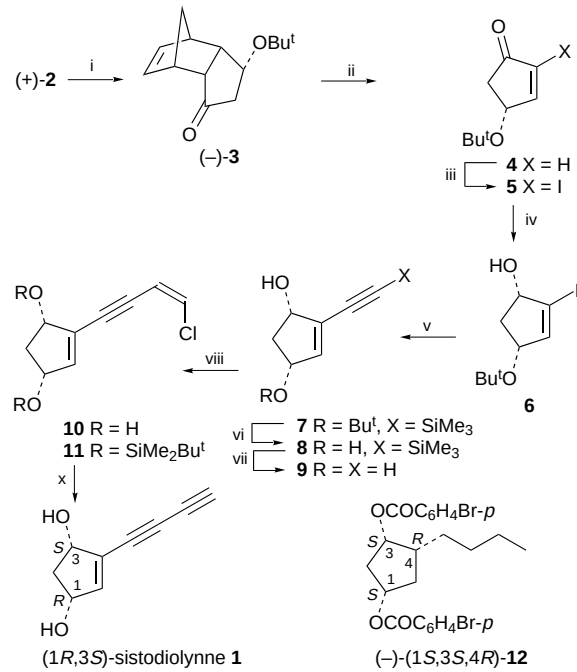
Sistodiolynne [(1*R*,3*S*)-4-butadiynylcyclopent-4-ene-1,3-diol] **1** is a metabolite of the wood rot decay fungus *Sistorema raduloides* (P. Karst) Donk which was recovered from indoor air of a museum in San Juan, Puerto Rico.[1] The compound **1** proved to be extremely air-sensitive and only stable in solution. It has been shown by labelling experiments that it arises from five acetate units with loss of a methyl carbon from one of the acetate units during the biosynthesis. Its structure was determined by spectroscopic methods, mainly, NMR, and the absolute configuration was proposed by circular dichroism of the di(4-bromobenzoate) of the perhydro derivative of the natural product. In relation to our recent synthesis of chiral cyclopentenone building blocks,[2,3] we were interested in converting our chiral cyclopentenol block **2** into sistodiolynne **1** so as to establish an enantiocontrolled synthesis and to confirm the proposed structure. Here we report the first construction of sistodiolynne **1** and the all-*cis* di(4-bromobenzoate) (−)-**12** of the perhydro derivative of **1**, which verified the proposed structure for the natural product (Scheme 1).

The optically pure tricyclic alcohol[2] (+)-**2**, $[\alpha]_D^{28}$ +75.4 (*c* 1.2, $CHCl_3$), mp 95 °C, obtained by lipase-mediated kinetic resolution,[2] was first transformed into the (*R*)-cyclopentenone[2,4] **4**, $[\alpha]_D^{28}$ +53.2 (*c* 0.9, MeOH), in 72% overall yield *via* the tricyclic ketone (−)-**3**, $[\alpha]_D^{26}$ −186.6 (*c* 1.0, $CHCl_3$), by sequential oxidation and thermolysis (Scheme 2). Although optically active **4** may be obtained more directly from the cyclopentenol precursor by a similar lipase-mediated resolution[2] or from racemic **4** by chemical resolution,[4] the present procedure seemed more appropriate with respect to the optical purity of the product. Exposure of **4** to iodine in the presence of pyridine[5] gave the air sensitive α-iodo enone **5**, which was immediately reduced with sodium borohydride–cerium(iii) chloride[6] to give stereoselectively *cis*-4-*tert*-butoxy-2-iodocyclopent-2-enol†‡ **6**, $[\alpha]_D^{28}$ +41.0 (*c* 0.9, $CHCl_3$), mp 90–92.5 °C, as a single product in 92% overall yield from **4**. The stereochemistry of **6** was determined by a NOE experiment on the benzoate of **6**, which exhibited significant interaction between the C(1) (δ_H 5.70) and C(4) (δ_H 4.54) protons. Moreover, the stereochemistry of **6** was confirmed unambiguously by converting it into *cis*-4-*tert*-butoxycyclopent-2-enol[2] in 80% yield on exposure to *tert*-butyllithium followed by acetic acid in tetrahydrofuran (THF) at −78 °C. A cross-coupling reaction[7,8] between **6** and trimethylsilylacetylene proceeded without difficulty using dichlorobis(triphenylphosphine)palladium(ii) $[PdCl_2(PPh_3)_2]$[9] as catalyst in the presence of copper(i) iodide in triethylamine to give the enyne **7**, $[\alpha]_D^{28}$ +70.2 (*c* 1.4, $CHCl_3$), in 96% yield. To remove the two different protecting groups, **7** was sequentially exposed to titanium(iv) chloride[2,10] and tetrabutylammonium fluoride to give *cis*-1-ethynylcyclopent-1-ene-3,5-diol **9**, $[\alpha]_D^{25}$ −40.8 (*c* 0.5, $CHCl_3$), in 70% overall yield *via* **8**.

Very fortunately, a mild two-step construction of a 1,3-diyne functionality from a terminal acetylene exists.[11] To apply this procedure, **9** was first coupled with *cis*-1,2-dichloroethylene in the presence of tetrakis(triphenylphosphine)palladium(0)[12] in butylamine to give the dienynediol **10**, accompanied by a trace of inseparable phenylphosphine impurities, which was isolated in the pure state as the di(*tert*-butyldimethylsilyl) ether **11**, $[\alpha]_D^{27}$ −43.8 (*c* 0.3, $CHCl_3$), by treating the mixture with *tert*-butyldimethylsilyl chloride in the presence of imidazole. The overall yield of **11** from **9** was 71%. Exposure of **11** to tetrabutylammonium fluoride (5 equiv.) in THF at room temperature[11] for 10 h furnished sistodiolynne **1** as a highly unstable oil by concurrent desilylation and dehydrochlorination. Although the product generated could not be isolated in a pure



Scheme 1



Scheme 2 *Reagents and conditions*: i, SO_3·pyridine, Me_2SO, Et_3N, room temp. (94%); ii, *o*-dichlorobenzene, 180 °C, 2.5 h (77%); iii, I_2, pyridine, CH_2Cl_2; iv, $NaBH_4$–$CeCl_3$, MeOH, −78 °C (92% from **5**); v, CH≡CSiMe$_3$, $PdCl_2(PPh_3)_2$ (6 mol%), CuI (8 mol%), Et_3N, 4 h (96%); vi, $TiCl_4$, CH_2Cl_2, 0 °C, 2 min; vii, Bu_4NF, THF, room temp. (70% from **8**); viii, (*Z*)-ClHC=CHCl, $Pd(PPh_3)_4$ (5 mol%), CuI (15 mol%), $BuNH_2$, benzene, 0.5 h; ix, Bu^{t}Me$_2$SiCl, imidazole, DMF (71% from **9**); x, Bu_4NF (5 equiv.), THF, room temp., 10 h

state as it polymerised even in a solution during purification as described,[1] its ^{1}H NMR spectrum measured directly [in $(CD_3)_2CO$] was identical to that of the natural product.[1]

On the other hand, **11** was hydrogenated under medium-pressure conditions in the presence of palladized carbon to convert it into the mixture containing the stable perhydro derivative of the natural product **1** as the major product. The major product isolates as the di(4-bromobenzoate) **12**, after desilylation and 4-bromobenzoylation, had a circular dichroism (CD) spectrum, showing the first Cotton effect (negative) at 251 nm and the second (positive) at 234 nm, which was identical to that reported for **12** having the 1*S*,3*S*,4*R* configuration (negative at 251 nm and positive at 231 nm) originated from the natural product **1**. This indicated the stereochemistry of sistodiolynne **1** to be 1*R*,3*S* as proposed.

In summary, we could not isolate sistodiolynne **1** in a pure form owing to its intrinsic instability, however, the present synthesis verified the correctness of the proposed structure of the natural product made by spectroscopic methods.

Footnotes

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† Spectral (IR, ^{1}H NMR, mass and analytical (combustion and/or high resolution mass) data were obtained for all isolable compounds.

‡ *Selected data* for representative compounds. For **6**: δ_H (300 MHz, $CDCl_3$) 6.23 (1 H br s), 4.41 (2 H, m), 2.73 (1 H, dt, *J* 14, 7 Hz), 1.71 (1 H, dt, *J* 14, 5 Hz), 1.10 (9 H, s). For **11**: δ_H (300 MHz, $CDCl_3$) 6.36 (1 H, d, *J* 7.3 Hz), 6.12 (1 H, d, *J* 1.8 Hz), 5.98 (1 H, d, *J* 7.3 Hz), 5.05 (1 H, br s), 4.98 (1 H, br s), 2.03 (2 H, m), 0.89 (9 H, s), 0.87 (9 H, s), 0.1 (6 H, s), 0.06 (6 H, s). M^+, 412.2017; $C_{21}H_{37}O_2Si_2{}^{35}Cl$ requires M^+, 412.2022. For **1**: δ_H [300 MHz, $(CD_3)_2CO$] 6.32 (1 H, s), 4.65 (2 H, m), 4.46 (1 H, d, *J* 6.5 Hz), 4.17 (1 H, d, *J* 6.5 Hz), 3.27 (1 H, s), 2.70 (1 H, ddd, *J* 13.2, 7.3, 7.3 Hz), 1.45 (1 H, *J* 13.2, 6.0, 6.0 Hz). M^+, 148.0494; $C_9H_8O_2$ requires M^+, 412.2022. For **12**: δ_H (300 MHz, $CDCl_3$) 7.90 (2 H, d, *J* 8.5 Hz), 7.74 (2 H, d, *J* 8.5 Hz), 7.58 (2 H, d, *J* 8.5 Hz), 7.46 (2 H, d, *J* 8.5 Hz), 5.42 (1 H, m), 5.38 (1 H, m), 2.60 (1 H, dt, *J* 13.5, 7.5 Hz), 2.42 (1 H, ddd, *J* 16, 8.0, 5.0 Hz), 2.19 (1 H, br d, *J* 16 Hz), 2.0 (1 H, m), 1.3–1.8 (7 H, m), 0.92 (3 H, br t, *J* 7.0). M^+, 522.0048; $C_{23}H_{24}O_4{}^{79}Br_2$ requires M^+, 522.0041.

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Received in Cambridge, 8th January 1997; Com. 7/00186J