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Synthesis of Dihydrooxepin Models Related to the Antitumor Antibiotic MPC1001

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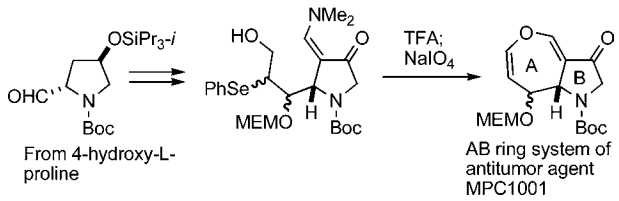
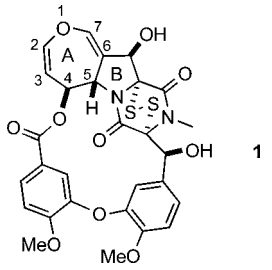
ABSTRACT



4-Hydroxy-L-proline was converted into the tetrahydrooxepino[4,3-*b*]pyrrole ring system characteristic of the potent antitumor agent MPC1001. Key steps were regioselective formation of a vinylogous amide by use of Bredereck's reagent and acid-induced cyclization of an alcohol onto the carbon–carbon double bond of that amide by addition–elimination to generate the seven-membered oxacyclic subunit.

MPC1001 (**1**)[1] is a member of a small group of structurally complex fungal metabolites containing both dihydrooxepin and dithiopiperazinedione subunits. Other members of this group include the very closely related emestrin[2,3] (MPC1001 is an *O*-methyl derivative of emestrin), aranotin[4,5] (and its acetate[5] and several other acylated derivatives[6,7]), the emethallicins,[8] and a number of partially deoxygenated analogues[1b] of MPC1001. Most of these compounds have important biological characteristics that include, depending on the particular substance, activity against viruses,[4b,5c] bacteria,[1a,3,7] and fungi,[2] the ability to inhibit epidermal growth factor[6] and compound 48/80-induced histamine release,[8] as well as antimalarial[7] and anticancer[1] properties. MPC1001 itself is



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especially noteworthy because it suppresses the proliferation of a human prostate cancer cell line (DU145) to an extent that is considerably more potent (2- to 40-fold) than that exerted by adriamycin, mitomycin C, or etoposide;[1a] the IC_{50} values for MPC1001 and the other three substances are 9.3, 20, 25, and 400 nmol/mL, respectively.

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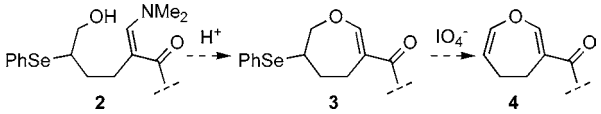
The complex structure and impressive anticancer activity of MPC1001 clearly mark it as an important synthetic target. However, neither this compound nor any of the related dihydrooxepin natural products have been reached by synthesis, although much helpful background information is available because the construction of dithiopiperazine-diones has been studied within the context of natural product synthesis, as well as in its own right.[9,10] Several methods are also known for making 4,5-dihydrooxepins,[11,12] the most general and effective being thermal Cope rearrangement of *cis*-divinyl epoxides.[12]

We report here the synthesis of the AB ring system of MPC1001 in which we use a new approach to dihydrooxepins. Our route to the 7-membered ring (Scheme 1) is

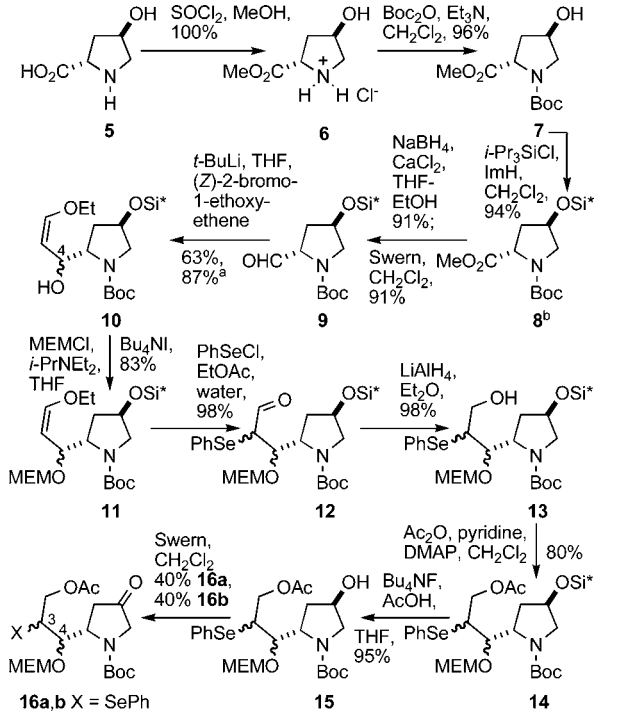
Scheme 1. Formation of Dihydrooxepin



based on intramolecular addition−elimination along the lines **2** → **3**, followed by introduction of a double bond (**3** → **4**), using selenoxide fragmentation.

The starting point was commercially available 4-hydroxy-L-proline **5**, which was converted by conventional methods[13,14] into the fully protected derivative **8** (Scheme 2), and the ester group was then changed into an aldehyde[15] by reduction to the alcohol level and reoxidation (**8** → **9**), so as

Scheme 2. Elaboration of 4-hydroxyproline



[a] Corrected for recovered starting material. [b] Si* = $SiPr_3$-*i*.

to set the stage for introduction of the C(1)−C(3) segment of the dihydrooxepin ring. To this end, aldehyde **9** was treated with (*Z*)-2-ethoxyvinyllithium[16,17] to afford the C(4) epimeric alcohols **10** (ca. 1:1), which were protected as their MEM ethers. Attempts to attach other protecting groups (MOM or Bn) were unsuccessful, but were not studied exhaustively, as use of MEMCl was successful at the first attempt. Neither the alcohols **10** nor the derived MEM ethers **11** could be separated, but this is of little consequence. Addition of PhSeCl smoothly produced the α-(phenylseleno) aldehydes **12**, which were reduced ($LiAlH_4$) and acetylated (**12** → **13** → **14**). It was important to use $LiAlH_4$ for the reduction[18] as $NaBH_4$ caused extensive loss of the PhSe group. Finally, the silicon protecting group was removed to release alcohols **15**. These are key intermediates because the selenium-containing side chain now has all the necessary atoms as well as suitable functionality to generate the segment labeled 1−4 in structure **1**.

Alcohols **15** were subjected to Swern oxidation, and the resulting ketones **16a**,**b** could be separated into a more polar (**16a**) and a less polar (**16b**) fraction. Each contained two C(3) isomers but this fact was obscured because slow rotation about the N−C(O) bond seriously complicated the NMR spectra. The stereochemistry at C(3) ultimately becomes

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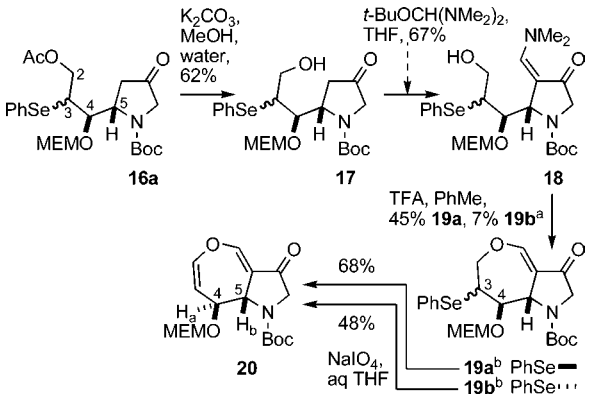
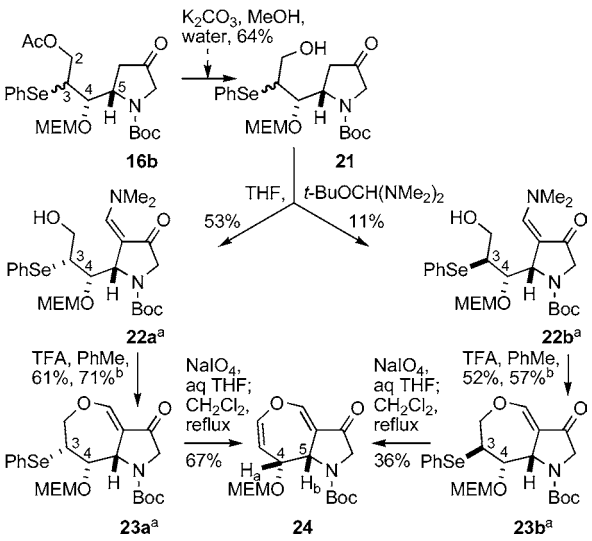
Scheme 3. Formation of Dihydrooxepin



[a] Total yield of **19a**,**b** is 60% after correction for recovered **18**. [b]Stereochemical assignment at C(3) is arbitrary.

irrelevant as that center is converted to sp^2 hybridization. However, the spectral complexities disappear at a later stage of the synthesis, and allow stereochemical assignment, at least for C(4) (see Schemes 3 and 4).

Scheme 4. Formation of Dihydrooxepin



[a] Stereochemical assignment to C(3) is arbitrary. [b] Corrected for recovered starting material.

Deacetylation (Scheme 3, **16a** → **17**) and treatment with Bredereck's reagent[19,20] [*t*-BuOCH(NMe_2)$_2$] produced two inseparable isomers of the vinylogous amide **18**, for which we show an arbitrary *Z* geometry for the carbon−carbon double bond. We had initially used $Me_2NCH(OMe)_2$ but both the yield and conversion were poor with this reagent. When **18** was exposed to the action of CF_3CO_2H an addition−elimination sequence took place to generate a 6.7:1 mixture of the bicyclic ethers **19a** and **19b**. These compounds, which were easily separated, must differ in stereochemistry at C(3); however, we could not assign the stereochemistry, and that shown is arbitrary. The less polar isomer (**19a**) was subjected to selenoxide fragmentation to give the AB ring model **20**. The more polar isomer (**19b**) was also converted into **20** by selenoxide fragmentation, although in lower yield (48% versus 68%). Because selenoxide fragmentation is normally a *syn* elimination, we suspect that the higher yielding process **19a** → **20** has the PhSe group *syn* to the C(4) oxygen, so that only one pathway for *syn* fragmentation is available, and that the conversion of **19b** into **20** is lower yielding because two *syn* fragmentations occur, only one of which affords **20**. However, we do not have experimental evidence to support this interpretation, and have to regard our stereochemical assignments to C(3) as little better than arbitrary.

The less polar fraction (**16b**) resulting from the original Swern oxidation of **15** (see Scheme 2) was subjected to an entirely comparable set of reactions (Scheme 4): hydrolysis of the acetate afforded a mixture of isomeric alcohols **21** and, when treated with Bredereck's reagent, these gave a 4.8:1 mixture of *separable* vinylogous amides **22a** (less polar and major product) and **22b** (more polar), to which we again arbitrarily assign the indicated C(3) stereochemistries. The major product, on treatment with CF_3CO_2H, afforded the bicyclic compound **23a** and, when this was subjected to selenoxide fragmentation, it gave the AB ring system **24**. The minor product **22b** from the reaction with Bredereck's reagent also gave **24** when subjected to the same sequence of reactions.

We observed a strong NOE between H_a and H_b in **24** and a barely discernible NOE between the corresponding hydrogens in **20**; on this basis we assign to **20** and **24** the indicated stereochemistry at C(4). That stereochemistry could not be deduced from the spectra of the precursors, but once the assignment to **20** and **24** had been made, we could infer that the same stereochemistry applies to these precursors. The model compound **20** has the same relative and absolute stereochemistry as the natural product,[1] while the other model **24** would require inversion at C(4) to attain the natural stereochemistry.

In summary, we have developed a route to the AB ring system of MPC1001 that involves an unusual method for constructing the dihydrooxepin substructure. The approach depends on the presence of the B ring, which is itself provided by a starting material from the chiral pool.

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Supporting Information Available: Experimental procedures, and spectral data as well as copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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