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Synthesis of a monocyclic core of the antifungal sordarins

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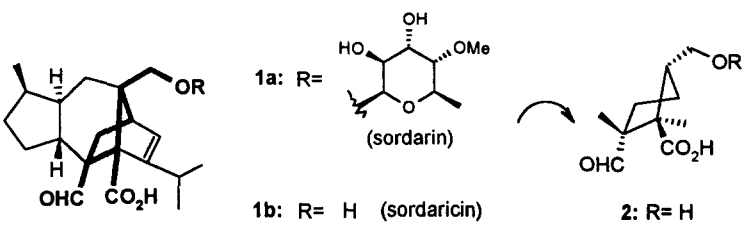
Abstract: An enantiospecific synthesis of a monocyclic core of the antifungal sordarins and sordaricins has been achieved. This synthesis is based on the conversion of (+)-3,9-dibromocamphor into a 1,1,2,2,5-pentasubstituted cyclopentane bearing all the key functionalities present in these antifungals.

Keywords: *antifungals; cyclopentanes; enantiospecificity*

Sordarin (**1a**) and sordaricin (**1b**) derivatives are selective and potent fungal protein synthesis inhibitors[1]. They are also capable of inhibiting the growth of the most common fungal pathogens and are considered as promising antifungal agents[2]. As part of a chemical program aiming to develop new and more efficient antifungals based on these molecules, we decided to determine the smallest part which retained inhibitory activity of the fungal protein synthesis. An approach was the reduction of the tetracyclic aglycone to a cyclopentane **2** containing all the key functionalities which make up its pharmacophore: the aldehyde, the carboxy and the methyleneoxy groups. (Scheme 1)

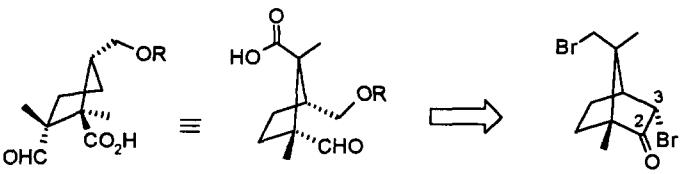


Scheme 1

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01910-8

The cyclopentane OHC-C-C-CO_2H dihedral angle in our analogue must be very close to that within of the tetracyclic terpene[3]. On the other hand the presence of methyl groups in the α-positions of the aldehyde and carboxy groups should avoid α-epimerization.

Thus we considered a chiral monoterpene source and envisaged that a functionalized camphor such as **3** would render the desired substituted cyclopentane through a key oxidative cleavage of the camphor C2-C3 bond. Further functional group transformations would give access to **2**.(Scheme 2)

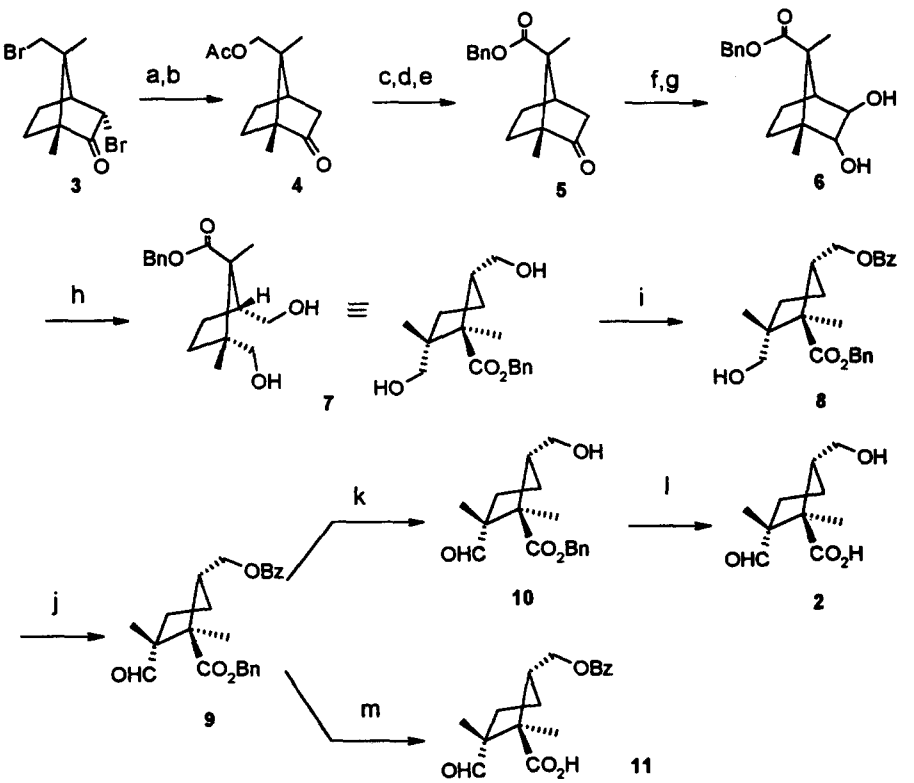


2 **3**

Scheme 2

The synthetic route is depicted in scheme 3. Thus, (+)-3,9-Dibromocamphor **3**[4] was transformed into the acetate **4** in two steps: reductive α–bromine elimination[5] and displacement of bromide by acetate[6]. Saponification of **4** and oxidation to the carboxylic acid[7], followed by benzylic esterification afforded the C-9 functionalized camphor ketone **5**. Oxidation of this ketone to the corresponding camphorquinone with selenium dioxide[8] and reduction of this diketone with sodium borohydride led to the 1,2-diol **6** (mixture of diastereomers) which was subjected to typical oxidative cleavage conditions (periodic acid in tetrahydrofuran) followed by *in situ* borohydride reduction to give the diol **7**[9]. At this point, regioselective functionalization of the least hindered alcohol and the re-oxidation of the other to an aldehyde was needed to complete the synthesis of our pharmacophore model. Thus, benzoylation of **7** (benzoyl chloride, DMAP) in dichloromethane at -40°C afforded the benzoate **8** in 44 % yield. Oxidation (PCC) converted the alcohol **8** into the aldehyde **9** which upon selective ester hydrolysis gave **10**. Finally, debenzylation of **10** (H_2, Pd/C) led to the simplified sordaricin analogue **2**.

^{1}H-NMR spectra of both **10** and **2** show mixtures of open aldehyde and cyclic hemiacetal isomers in a 1:1 ratio. In order to obtain a derivative having a frozen cyclopentane ring, compound **9** was debenzylated (H_2, Pd/C) to give **11** which presents an open 1,2 OHC-CO_2H substructure on the basis of its spectroscopical data.(Scheme 3)



a) Zn, AcOH, rt, 90%; b) CsOAc, DMF,110°C, 96%; c) LiOH, THF/H_2O, rt, 93%; d) CrO_3, $MnSO_4$, aq.H_2SO_4, 80%; e) DBU, BnBr, MeCN, rt, 87%; f) SeO_2, Ac_2O, 145°C, 80%; g) $NaBH_4$, aq.EtOH, rt, 74%; h) H_5IO_6, THF, rt; $NaBH_4$, aq.EtOH, rt, 80%; i) BzCl, CH_2Cl_2, DMAP, -40°C, 44%; j) PCC, CH_2Cl_2, rt, 90%; k) LiOH, THF/H_2O/MeOH, rt, 90%; l)H_2, Pd/C, EtOAc , 42%; m) H_2, Pd/C, EtOAc, 60%

Scheme 3

In conclusion, this work constitutes a practical example of the application of the chiral camphor source to the preparation of new chiral compounds[10,11]. This route is currently being applied to the obtention of other derivatives presenting this simplified sordarin pharmacophore. Antifungal activity results will be reported elsewhere.

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References and notes:

[1] Domínguez JM, Capa L, Serramía MJ, Mendoza A, Viana JM, García-Bustos JF, Martín JJ. Abstracts of Papers. 37th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Toronto, ON, 1997; F-55.

[2] Herreros E, Martínez CM, Almela MJ, Lozano S, Gómez de las Heras F, Gargallo D. Abstracts of Papers. 37th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Toronto, ON, 1997; F-57.

[3] The moiety OHC-C-C-CO_2H is certainly uncommon since this functional grouping is normally found as cyclic hydroxylactone. Its presence in these molecules is likely due to a high dihedral angle (67° for sordaricin and 95° for its cyclopentanic analogue). These structures were modelled and conformationally optimized by semi-empirical methods.

[4] Commercially available (Aldrich Chem. Co.)

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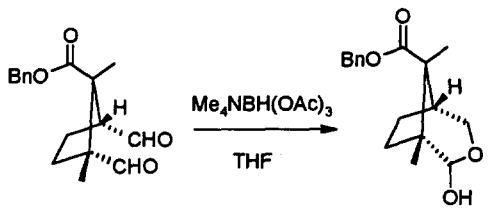
[6] Huffman JW, Desai RC. Synth. Commun. 1983: 553-557.

[7] Corey EJ, Ohno M, Chow SW, Scherrer RA. J. Am. Chem. Soc. 1959; 81: 6305-6309.

[8] Evans WC, Ridgion JM, Simonsen JL. J. Chem. Soc. 1934: 137. This alternative conversion (α-keto debromination and oxidation) proved to give better results than direct oxidation (KI/Na_2CO_3/DMSO) reported by Bauer and Macomber (Bauer DP, Macomber RS. J. Org. Chem. 1975; 13: 1990-1992).

[9] The regioselective reduction of the least hindered formyl group of the dialdehyde intermediate with a mild borohydride like $Me_4NBH(OAc)_3$ gave rise to a mixture of reduced compounds. Hemiacetal **13** could only be isolated in 28% yield.



12 **13**

[10] For the use of natural camphors in the synthesis of chiral natural products, see: Money T. Nat. Prod. Rep. 1985;2: 253-289.

[11] All new compounds gave satisfactory spectroscopic and analytical data.