Chimia 53 (1999) 222–223

ISSN 0009-4293

Isolation and Synthesis of Bioactive Compounds

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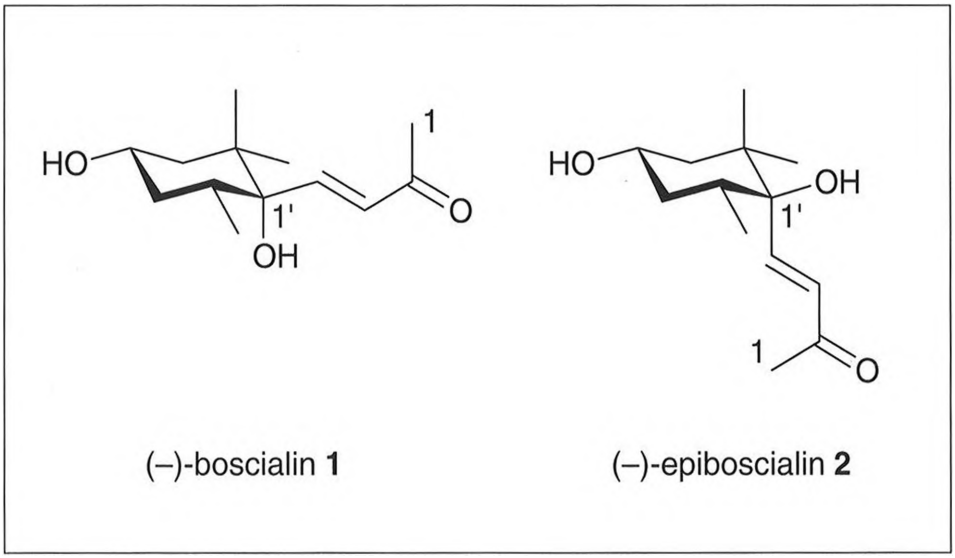
Abstract. Our interest in natural products and related bioactive compounds is illustrated by a few representative examples. Boscialin, a constituent of an African medicinal plant, and two furanones from a *Streptomyces* strain were isolated and their structures elucidated. The compounds were eventually synthesized for the determination of their absolute configurations and biological properties. Finally, the synthesis of some potential protein tyrosine-kinase inhibitors is discussed.

Urs Séquin grew up in Basel and studied chemistry at the University of Basel, where he received his Ph.D in 1970 with *C. Tamm*. From 1973 to 1974, he worked as a postdoctoral fellow with *A.I. Scott* at Yale University. He then returned to the University of Basel and got his Habilitation in 1976. In 1990, he was promoted to Professor. Further details of his research interests are to be found at http://www.chemie.unibas.ch/OC/Sequin/sequin.html.

Our research is focused, on one hand, on the isolation, structure elucidation, and synthesis of natural products from medicinal plants and from microorganisms. A second field of interest is the synthesis of potential protein tyrosine-kinase inhibitors. The few selected results from our laboratory given below illustrate these topics.

Plants and microorganisms have always been inspiring sources of natural products with new structures and interesting biological properties. With microorganisms that are pathogenic to humans becoming increasingly resistant towards the classical families of antibiotics, the search for new antimicrobially active substances is today of prime importance in medicinal chemistry. Some years ago, we isolated from the leaves of *Boscia salicifolia* Oliv., an African medicinal plant, the C_{13}-norisoprenoid (–)-boscialin **1** and its glucoside [1]. The compounds were isolated in very small amounts so that only the constitutions and relative configurations could be elucidated by NMR spectroscopy. In order to determine the absolute configuration and the biological activity of **1**, we undertook its synthesis. Starting from 2,2,6-trimethylcyclohexane-1,4-dione, a commercially available chiral building block, (–)-boscialin **1** and its 1'-epimer, (–)-epiboscialin **2**, could be obtained [2]. A slight variation of the procedure led to the two corresponding enantiomers. The natural (–)-boscialin and its epimer were found to inhibit the growth of the bloodstream forms of *Trypanosoma brucei rhodesiense* (the parasite causing sleeping sickness), whereas the two enantiomers proved to be inactive. In addition, all four compounds showed a slight cyto-



(–)-boscialin **1** (–)-epiboscialin **2**

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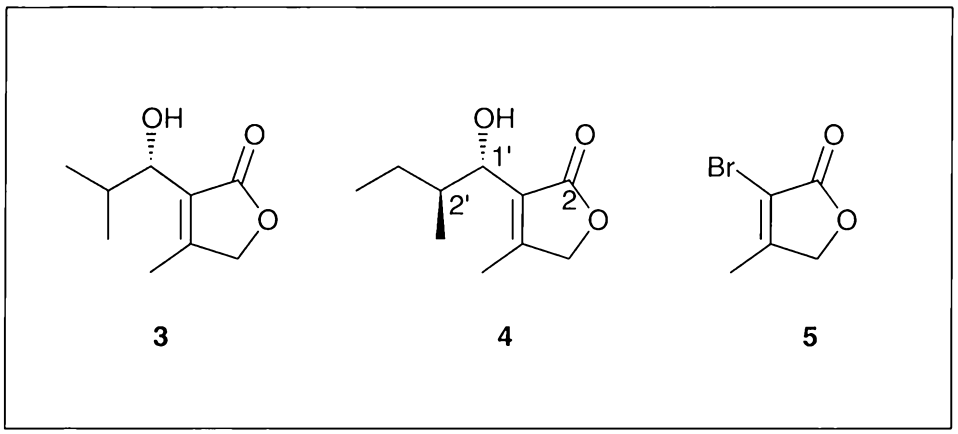

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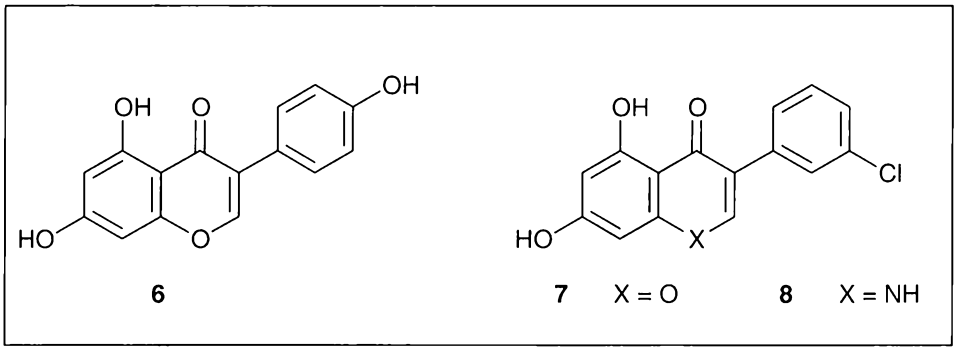

6 7 X = O 8 X = NH

toxicity and rather broad but modest antimicrobial activity.

The photoconductivity screening [3] of the fermentation broth of *Streptomyces antibioticus* TÜ 99 indicated the presence of some new metabolites. Workup led to several compounds, among which were the two 2(5*H*)-furanones **3** and **4** [4]. These compounds resemble somewhat the so-called A-factors, which control antibiotic production, cell differentiation, sporulation, and antibiotic resistance in *Streptomyces*. It, therefore, seemed attractive to synthesize these compounds. The starting point was the bromolactone **5**, for which a more efficient synthesis was developed. Lithiation of **5** followed by reaction with either 2-methylpropanal or (*S*)-2-methylbutanal gave racemic **3** and the two 1'-epimers with the constitution of **4**, respectively. This procedure has the advantage that similar furanones, which differ only in the constitution of the side chain, are readily accessible. The drawback is, of course, the loss of stereocontrol for C(1').

Esterification of racemic **3** with *Mosher*'s reagent (3,3,3-trifluoro-2-methoxy-2-phenylpropionyl chloride) and subsequent HPLC-separation, analysis of the ^{1}H-NMR spectra, and X-ray crystallography allowed us to assign the (*S*)-configuration to the metabolite **3**. Similar procedures revealed the absolute configurations of the chiral centers of furanone **4** to be (1'*S*,2'*S*) [5]. Preliminary biological tests indicated that metabolite **4** had some activity against *Pseudomonas aeruginosa* and was a weak inhibitor of the chitinase of *Serratia marcescens*.

Protein tyrosine kinases (PTKs) play a major role in pathways transducing extracellular signals to the cell nucleus. Overexpression or amplification of such kinases may be responsible for uncontrolled cell proliferation. Therefore, these enzymes are interesting targets for the synthesis of inhibitors that might have therapeutic potential in the treatment of malignant or non-malignant proliferative diseases such as cancer or psoriasis.

In recent years, we synthesized a series of compounds, which should mimic the transition state of the phosphorylation and, thus, might be tyrosine kinase inhibitors. We used β-nitrostyrene derivatives – as the tyrosine substitute – connected to an adenosine derivative through glutaric acid – the triphosphate mimic [6]. Compounds of this type proved to be active inhibitors (IC_{50} around 1 μM) of the PTK part of the epidermal growth-factor receptor.

A different approach consisted in the synthesis of analogs of known, relatively simple inhibitors of PTK, such as the isoflavonoid genistein **6** We, therefore, synthesized a number of isoflavones and quinolones resembling **6** [7]. Some of them showed remarkable inhibitory activities, surpassing that of genistein **6**: compound **7** has an IC_{50} value of *ca.* 0.1 μM towards the EGF-receptor PTK whilst compound **8** exhibits an IC_{50} of 8 nM.

This short report is the result of the skillful contributions of many co-workers to whom I am very grateful. The work was supported by the *Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung* (grant 20-49'045.96) and by *Novartis Pharma AG*.

Received: February 26, 1999

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