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[A0039]

Synthesis of Optically Active n-Alkyloxycatechols as Inhibitors of Lipoxygenase

Mathias Juch and Peter Rüedi*

Institute of Organic Chemistry, University of Zurich,Winterthurerstrasse 190, CH-8057 Zurich, Switzerland
Tel.: +41 1-2574241 Fax: +41 1-3619895, e-mail: peru@oci.unizh.ch,
http://www.unizh.ch/oci/persons/ruedi.html

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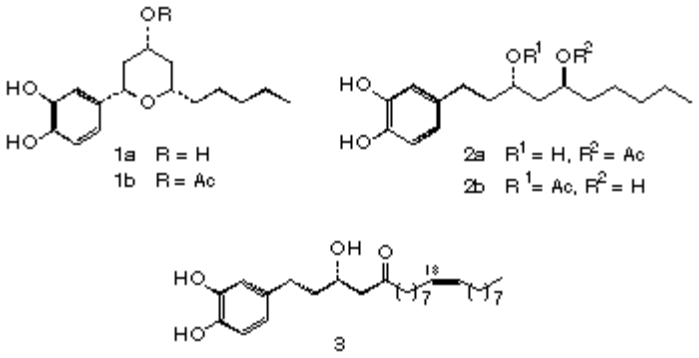
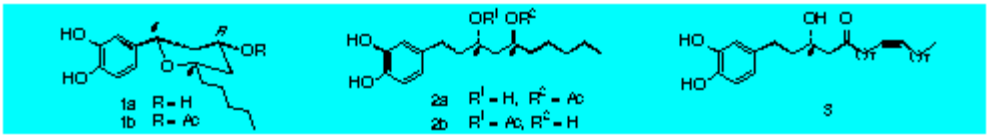
Abstract: Antioxidant activitv guided fractionation of extracts of *Plectranthus sylvestris* (labiatae) yielded the novel alkyloxycatechols **1**-**3** (M. Juch, P. Rüedi, *Helv. Chim. Acta* **1997**, *80*, 436). The optically active natural products and several diastereomers have been synthesized. The open chain compounds are prepared by enantioselsective reduction of the corresponding aldol adduct and chromatographic separation of the diastereomers, the cyclic ones by biomimetic phenol oxidation of **2b**.



Apart from their antioxidative activity (similar to BHA and BHT), the catechols are *in vitro* inhibitors of lipoxygenase exhibiting IC_{50}-values from the umol (**1** und **2**; similar to nordihydroguaiaretic acid and indomethacin) to the nmol range (**3**).

Introduction

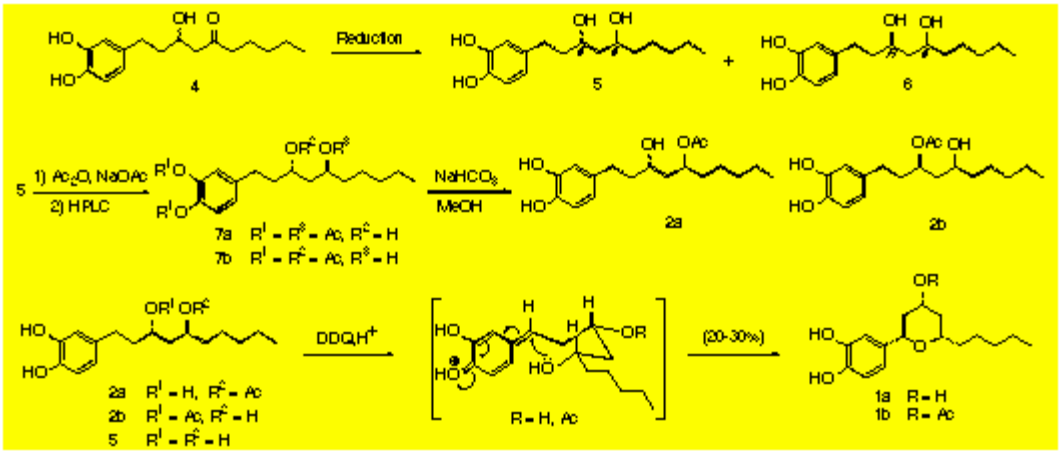
In the course of our current research program concerning genuine constituents of African and Asian labiatae species with respect to antioxidants, inhibitors of the arachidonate metabolism and allergens [1][2], antioxidative activity guided fractionation of extracts of *Plectranthus sylvestris* (GÜRKE) yielded the novel optically active alkyloxycatechols **1**-**3** [2]. The compounds are inhibitors of Lipoxygenase (LO). With the aim to investigate the influence of the chirality and functionality in the side chain concerning the LO inhibition, enantio- and diastereomeric catechols of this type are being prepared.



Synthesis

The monoacetoxy compounds **2a** and **2b** have been prepared by enantioselective reduction of the aldol **4** followed by acetylation and selective saponification of the phenolic acetoxy groups. The tetrahydropyrans **1a** and **1b** were obtained from **5** and **2a**/**2b,** resp. after biomimetic oxidation with 2,3-dichloro-5,6-

dicyano-1,4-benzoquinone (DDQ) [3]. The isomers **2a** and **2b** are separable by HPLC only after derivatization of the catechol moiety. In solution **2a** and **2b** undergo a slow 1,3-acyl shift (days) and the compounds can be oxidized with DDQ as a mixture which directly yields **1b**. Due to the conformatively favourable arrangement of the substituents (all equatorial), the ring closure to the natural 2,4,6-trisubstituted tetrahydropyran is exclusively observed. Attempts to saponify selectively the corresponding triacetates of **6** resulted in an equilibrium mixture as a consequence of a fast 1,3-acyl shift.



Reduction with baker's yeast	without D-(+)-saccharose	with D-(+)-saccharose	**Reduction with (*S*)-BINAP-Ru** [4]	10bar/100deg.C	20 bar/75deg.C
Reaction time	4 days	7 days	Reaction time	3 hrs	20hrs
Transformation	100%	100%	Transformation	100%	100%
Yield **5**; *ee* **5**	27 %; 0.82	32%; 0.54	Yield **5**; *ee* **5**	60 %; 0.55	65%; 0.54
Yield **6**; *ee* **6**	27 %; 0.86	25 %; 0.26	Yield **6**; *ee* **6**	40 %; 0.88	35 %; 0.98

The *ee*-determinations of **5** were performed on the mixture of the triacetates **7a** and **7b** (the corresponding triacetates of **6**, resp.) by HPLC on Chiralcel OD-H, 5u, 250^{x}4.6 mm, hexane/2-propanol 9:1. This procedure enabled a simultaneous double determination.

The synthesis of the enantiomeric compounds *ent*-**5** (3*R*,5*R*) and *ent*-**6** (3*S*,5*R*) is in current progress.

Inhibition of Lipoxygenase

In order to get preliminary information concerning a structure-activity relationship for the inhibition of LO, compounds with variations of the configuration and functionality in the side chain have been tested. The activity of the enzyme ('Soybean Lipoxydase', Sigma, Type I-B) was monitored by a spectrophotometrical assay related to [5][6]. The IC_{50}-values of the isolated alkyloxycatechols and of selected derivatives have been determined. The known anti-inflammatory and analgesic drugs nordihydroguaiaretic acid (NDGA) and indomethacin (INDO) were used as internal controls.

	1a	**1b**	**2a**	**2b**	**3**	**4**	**5**	**6**	**NDGA**	**INDO**
IC_{50} [mM]	74	9	50	71	0.09	78	285	175	54	181

References

[1] Ch. Bürgi, P. Rüedi, *Helv. Chim. Acta* **1993**, *76*, 1890. [4] G. Capozzi, S. Roelens, S. Talami, *J. Org. Chem.* **1993**, 58, 7932.

[2] M. Juch, P. Rüedi, *Helv. Chim. Acta* **1997**, *80*, 436. [5] J.C. Sircar, C.F. Schwender, E.A. Johnson, *Prostaglandins* **1983**, *25*, 393.

[3] Y. Oikawa, K. Horita, O. Yonemitsu, *Heterocycles* **1985,** 23, 553. [6] A.T. Evans, E.A. Formukong, F.J. Evans, *Biochem. Pharmacol.* **1987**, *36*, 2035.

Comments

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