interface of the membrane, while the peptide acyl chains are inserted into the interior of the membrane (Figure 3). The lipid/water interface of the membrane represents a broad zone containing disordered headgroups, glycerol, and upper chain segments, which is easily accessed by water molecules.[13]

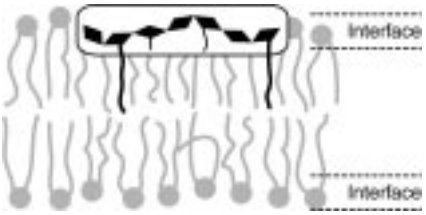

Figure 3. Schematic representation of the location of the Ras peptide in the lipid/water interface of the membrane (headgroup, glycerol, and upper chain region). The peptide acyl chains and hydrophobic side chains extend deeper into the hydrophobic part of the membrane.

The hydrophobic peptide side chains project into the acyl chain region of the membrane, where the low polarity environment allows favorable hydrophobic interactions with the lipid chains. The polar backbone of the peptide interacts strongly with the aqueous phase. For the peptide/lipid system investigated here a full assignment of the NMR signals as well as a quantitative analysis of the location and membrane-bound structure of the peptide appears to be feasible by using HR MAS NMR spectroscopy, thus providing more insight into this important mechanism for membrane binding and protein insertion.

Experimental Section

$[D_{67}]$1,2-Dimyristoyl-*sn*-glycero-3-phosphocholine ($[D_{67}]$DMPC) was used without purification. The lipid-modified N-Ras peptide was synthesized enzymatically as described before.[2] For the preparation of the NMR samples, phospholipid and peptide (molar ratio of 10:1) were combined in methanol, dried under a stream of nitrogen, dissolved in cyclohexane and lyophilized. The samples were hydrated to 30 wt% H_2O, freeze-thawed, stirred, and gently centrifuged for equilibration and transferred into spherical inserts for 4-mm MAS rotors. NMR experiments were carried out on a Bruker DRX600 spectrometer at a resonance frequency of 600.13 MHz at 37 °C. The MAS frequency was 12 kHz. Spectra were acquired at a spectral width of 10.9 kHz with a 90° pulse length of 6.2 μs. For phase-sensitive NOESY experiments (mixing time 200 ms) 400 complex data points were collected in the indirect dimensions with 32 scans per increment with a 4 s relaxation delay between successive scans.

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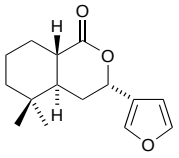
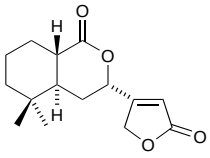
Enantioselective Synthesis of the Ricciocarpins A and B**

Christoph Held, Roland Fröhlich, and Peter Metz*

Dedicated to Professor Wittko Francke on the occasion of his 60th birthday

The furanosesquiterpene lactone ricciocarpin A (**1**) isolated from the liverwort *Ricciocarpos natans* exhibits high molluscicidal activity against the water snail *Biomphalaria glabrata*, one of the vectors of schistosomiasis (bilharziasis).[1] Though several syntheses were published for racemic **1**,[2]


ricciocarpin A (**1**)


ricciocarpin B (**2**)

no enantioselective version has so far been reported. Since the absolute configuration of **1** was unknown prior to our work, we principally wanted to devise an access to both enantiomers. Moreover, we were also interested in developing a first synthetic access to the structurally similar liverwort-constituent ricciocarpin B (**2**).[1] Our synthesis of **1** reported here relies heavily on the twofold application of the catalytic ring-closing metathesis (RCM)[3] to generate both six-membered rings of the target.

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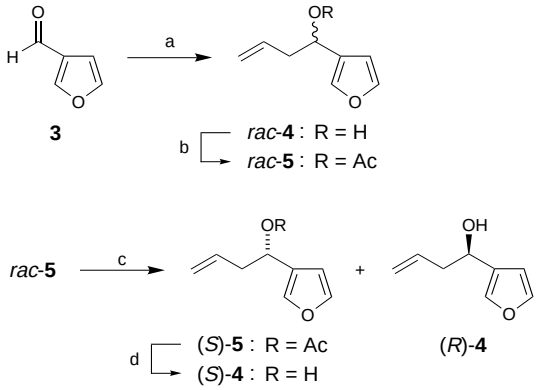
Furan-3-carbaldehyde (**3**), which has already been converted into both enantiomers of the homoallylic alcohol **4** by stoichiometric asymmetric allylborations, was used as the starting material[4] (Scheme 1). We investigated different

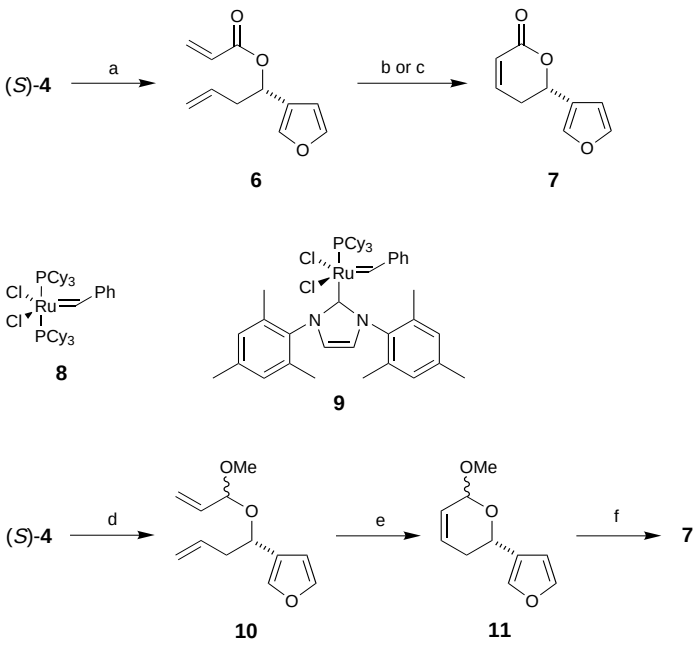


Scheme 1. a) Zn, CH_2=$CHCH_2Br$, NH_4Cl/H_2O/THF, 25 °C, 95 %; b) Ac_2O, NEt_3, DMAP, CH_2Cl_2, 25 °C, 95 %; c) lipase from *Alcaligines sp.*, H_2O/DMSO (10:1), pH 7, 25 °C, 44 % (*S*)-**5** (99 % *ee*), 48 % (*R*)-**4** (88 % *ee*); d) NaOH, 25 °C, 97 % (99 % *ee*). Ac = acetyl, DMAP = 4-dimethylaminopyridine.

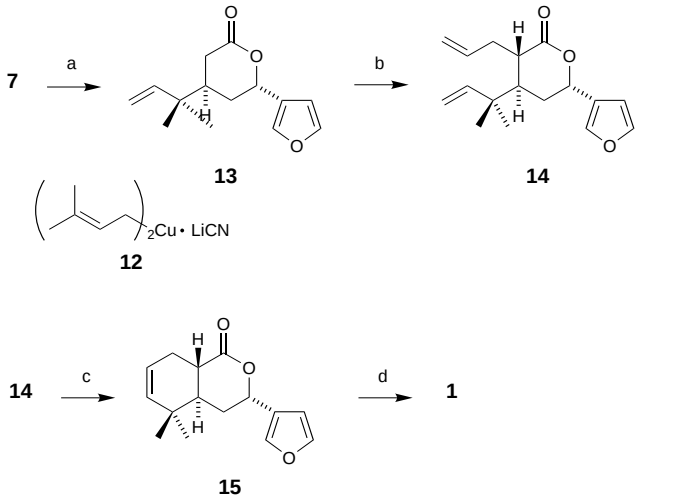
procedures for the enzymatic kinetic resolution of *rac*-**4** as well as of the derived acetate *rac*-**5** using commercially available esterases and lipases.[5] For the preparation of *rac*-**4**, aldehyde **3** was subjected to a Barbier reaction with allyl bromide and zinc.[6] Hydrolysis of *rac*-**5** catalyzed by a lipase from *Alcaligines sp.* gave the best results. In addition to (*R*)-**4** (88 % *ee* by GC), this protocol provided (*S*)-**5** (99 % *ee* by GC), which was transformed to (*S*)-**4** by alkaline hydrolysis after chromatographic separation from (*R*)-**4**. Thus, both enantiomers of **4** were at hand in high enantiomeric purity by asymmetric catalysis.

Alcohol (*S*)-**4** was converted into the acrylate **6** with acryloyl chloride (Scheme 2). Application of a reagent system[7] consisting of Grubbs' catalyst **8** and titanium tetraisopropoxide in the molar ratio 1/3 led to a 65 % yield of **7** when a relatively high catalyst loading was used. In the presence of 5 mol % of catalyst **9**, which exhibits an enhanced reactivity towards acrylates,[8] lactone **7** was obtained in 68 % yield. Transition to the less Lewis basic mixed acetal **10** promised a further improvement in the yield of the metathesis. Compound **10** was prepared in good yield by a palladium-catalyzed reaction of (*S*)-**4** with methoxyallene.[9] Use of the standard conditions for the RCM (5 mol % **8**, CH_2Cl_2, 25 °C, 2 h) resulted in a 98 % yield of acetal **11**. The high reaction rate allowed a reduction in the amount of catalyst **8** to only 0.75 mol % while maintaining a nearly equally high yield (95 %) of **11**. By omitting the solvent the reaction could be run at reduced pressure, which guaranteed an efficient removal of the ethene produced during the metathesis. A chemoselective oxidation[10] of acetal **11** to the unsaturated lactone **7** completed the alternative route to this crucial intermediate.

Lactone **7** was transformed to diene **14** through two allylation reactions (Scheme 3). First, a conjugate addition of cuprate **12**[11] to give lactone **13** took place with complete regio- and stereoselectivity, as monitored by capillary GC



Scheme 2. a) CH_2=$CHCOCl$, NEt_3, DMAP, CH_2Cl_2, 0 → 25 °C, 80 %; b) 10 mol % **8**, 30 mol % $Ti(OiPr)_4$, CH_2Cl_2, 40 °C, 65 %; c) 5 mol % **9**, CH_2Cl_2, 40 °C, 68 %; d) CH_2=C=CHOMe, 5 mol % $Pd(OAc)_2$/dppp, NEt_3, CH_3CN, reflux, 80 %; e) 0.75 mol % **8**, 0.5 mbar, 25 °C, 95 %; f) MoO_3, H_2O_2/THF, −5 → 25 °C, then Ac_2O, NEt_3, CH_2Cl_2, 0 → 25 °C, 75 %. Cy = cyclohexyl, dppp = 1,3-bis(diphenylphosphanyl)propane.

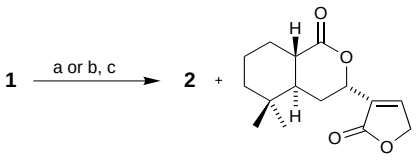


Scheme 3. a) **12**, THF, −78 °C, then NH_4Cl/H_2O, −78 → 25 °C, 65 %; b) LDA, THF, −78 °C, then CH_2=$CHCH_2Br$, −78 → 25 °C, 80 %; c) 1.5 mol % **8**, CH_2Cl_2, 25 °C, 97 %; d) 1 atm H_2, 10 mol % $[RhCl(PPh_3)_3]$, benzene, 25 °C, 97 %. LDA = lithium diisopropylamide.

analysis. The subsequent α-allylation, which yielded the substrate **14** for the second ring-closing metathesis, occurred only *trans* to the bulky dimethylallyl group. Again, no additional isomer could be detected by capillary GC. Diene **14** was subjected to an RCM under standard conditions, whereupon the cyclohexene **15** was isolated in high yield.[12] Since no reaction was observed between 3,3-dimethylbut-1-ene and **8** under similar conditions[13] the smooth conversion noted in our case is surely primarily a consequence of the intramolecular mode of attack on the sterically hindered olefin. Finally, homogeneous catalytic hydrogenation of

cyclohexene **15** led to (3*S*,4a*R*,8a*S*)-**1**, which proved to be identical (by comparison of optical rotation data) to the naturally occurring enantiomer of ricciocarpin A.[14] Hence we have developed a short, highly enantioselective and completely diastereoselective route to ricciocarpin A.

As ricciocarpin B (**2**) only differs from **1** within the five-membered ring, we tried to convert **1** into **2** by oxidation (Scheme 4). The bislactones **2** and **16** were obtained after



16

Scheme 4. a) 1 atm O_2, methylene blue, *hv*, MeOH, $-40\,^{\circ}C$, then $25\,^{\circ}C$; b) 1 atm O_2, methylene blue, DIPEA, *hv*, CH_2Cl_2, $-78\,^{\circ}C$, then $25\,^{\circ}C$; c) $NaBH_4$, MeOH, $25\,^{\circ}C$, 25% **2**, and 25% **16** from **1** by steps (a) and (c), 46% **2** by steps (b) and (c). DIPEA = diisopropylethylamine.

[4+2] cycloaddition with singlet oxygen and subsequent thermal decomposition of the primary adduct as well as reduction with sodium borohydride.[15, 16] By comparison of the analytical data with literature values[1a] **2** could be identified as ricciocarpin B.[17] To the best of our knowledge the transformation of **1** to **2** reported here constitutes the first synthesis of ricciocarpin B. A crystal structure analysis of **16** was accomplished, and the depicted absolute configuration was proven by anomalous X-ray diffraction.[18] Thus, this analysis also secures the configurational assignment for **4**, which so far relied on analogy to the outcome of related allylborations[4] or on observations that some hydrolases preferentially attack a certain enantiomer in a substrate-independent fashion.[5, 19] The formation of **16** could be completely suppressed by photooxygenation in the presence of a sterically demanding base,[20] and the yield of **2** raised to 46% (non-optimized).

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[12] **15**: A solution of diene **14** (247 mg, 0.9 mmol) in dry dichloromethane (10 mL) was treated with **8** (10.5 mg, 1.5 mol%). After stirring the mixture at room temperature overnight, the solvent was removed in vacuo, and the residue purified by chromatography over silica gel (pentane/diethyl ether 1/1) to yield 215 mg of **15** (97%): ^{1}H NMR (500 MHz, $CDCl_3$, $25\,^{\circ}C$, TMS): $\delta = 7.44$ (s, 1H; CH), 7.41 (s, 1H; CH), 6.39 (s, 1H; CH), 5.56 (ddd, $^3J(H,H) = 10$ Hz, $^3J(H,H) = 5$ Hz, $^3J(H,H) = 2$ Hz, 1H; CH), 5.42 (br. d, $^3J(H,H) = 10$ Hz, 1H; CH), 5.34 (dd, $^3J(H,H) = 9$ Hz, $^3J(H,H) = 4$ Hz, 1H; CH), 2.61 (ddd, $^3J(H,H) = 11$ Hz, $^3J(H,H) = 11$ Hz, $^3J(H,H) = 5$ Hz, 1H; CH), 2.44 (dddd, $^2J(H,H) = 18$ Hz, $^3J(H,H) = 5$ Hz, $^3J(H,H) = 5$ Hz, $^4J(H,H) = 1$ Hz, 1H; CH_2), 2.23 (dddd, $^2J(H,H) = 18$ Hz, $^3J(H,H) = 11$ Hz, $^3J(H,H) = 2$ Hz, $^4J(H,H) = 2$ Hz, 1H; CH_2), 2.11 – 1.99 (m, 2H; CH_2), 1.80 (ddd, $^3J(H,H) = 11$ Hz, $^3J(H,H) = 9$ Hz, $^3J(H,H) = 6$ Hz, 1H; CH), 0.99 (s, 3H; CH_3), 0.98 (s, 3H; CH_3); ^{13}C NMR (125.76 MHz, $CDCl_3$, $25\,^{\circ}C$, TMS): $\delta = 174.6$ (s), 143.7 (d), 139.6 (d), 137.7 (d), 124.7 (s), 122.6 (d), 108.4 (d), 72.1 (d), 39.5 (d), 36.4 (d), 36.1 (s), 29.6 (t), 27.9 (q), 27.1 (t), 22.1 (q).

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[14] Synthetic **1**: $[\alpha]_D^{20} = +18.1$ ($c = 1.18$ in CH_2Cl_2); natural **1**:[1a] $[\alpha]_D^{20} = +17.8$ ($c = 1.18$ in CH_2Cl_2).

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[17] Synthetic **2**: $[\alpha]_D^{20} = +6.3$ ($c = 0.7$ in CH_2Cl_2); natural **2**:[1a] $[\alpha]_D^{20} = +6.3$ ($c = 0.9$ in CH_2Cl_2).

[18] Crystal dimensions $0.40 \times 0.40 \times 0.20$ mm^3, monoclinic, space group $P2_1$ (No. 4), $a = 8.194(1)$, $b = 8.747(1)$, $c = 10.251(1)$ Å, $\beta = 112.81^{\circ}$, $V = 677.3(1)$ Å^3, $\rho_{calcd} = 1.296$ g cm^{-3}, $2\theta_{max} = 148.4^{\circ}$, $Cu_{K\alpha}$ radiation, $\lambda = 1.54178$ Å, $\vartheta/2\theta$ scans, $T = 223$ K, 2813 reflections measured, 2525 independent ($R_{int} = 0.021$), of which 2495 were observed [$I \geq 2\sigma(I)$], $\mu = 7.61$ cm^{-1}, absorption correction by ψ-scan data (min/max transmission 0.751/0.863), structure solution by direct methods, 175 refined parameters, hydrogen atoms were calculated and refined as riding atoms, $R = 0.030$, $wR^2 = 0.085$, max/min residual electron density 0.18/-0.13 e Å^{-3}, Flack parameter $-0.06(16)$. Programs used: Express, MolEN, SHELXS-97, SHELXL-97, and SCHAKAL. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-150983. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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