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A new convenient route to enantiopure 2-coumarinyloxypropanals: application to the synthesis of optically active geiparvarin analogues

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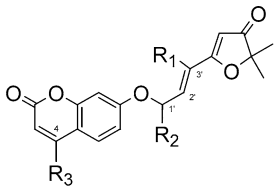
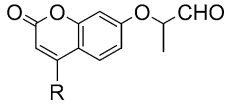
Abstract—A new convenient route to enantiopure 2-coumarinyloxypropanals is described: Rosenmund reduction of (*R*)- or (*S*)-2-coumarinyloxypropanoyl chlorides afforded in good yields the corresponding 2-coumarinyloxypropanals. Their subsequent aldolic condensation with 3(2*H*)-furanones, followed by dehydration, led to enantiopure geiparvarin analogues now being investigated as promising antitumoral compounds.

In our previous paper, we reported the synthesis of a series of geiparvarin analogues in which a hydrogen atom replaced the 3′-methyl group on the unsaturated alkenyloxy bridge, as well as geiparvarin (**1**) itself and evaluated their activities both against several human tumoral cell lines in vitro[1] and as powerful and highly selective monoamino oxidase-B (MAO-B) inhibitors.[2] Our study clearly showed that the elimination of the methyl group on the double bond remarkably increased the cytotoxic activity against all of the tumoral cell lines as well as the inhibitory power on MAO-B in comparison with the natural compound **1**. Although further experiments are needed, these results led us to hypothesize that a specific target might be involved in both pharmacological effects. At any rate, they suggested the need for a more thorough investigation of the potentiality of geiparvarin and its analogues as antitumoral drugs as well as of the related mechanism leading to apoptosis.

The ability of these compounds to act as alkylating agents by means of conjugate addition (Michael acceptors) is well known and seems to be related to their biological activity.[3] In order to study the structure–activity relationships of geiparvarin analogues we undertook the synthesis of the first optically active geiparvarin demethylated at the 3′ position (compounds **2** and **3**).





1 R_1=Me, R_2=R_3=H (**Geiparvarin**)
2a R_1=R_3=H, R_2=Me (*R*)
2a R_1=R_3=H, R_2=Me (*S*)
3a R_1=H, R_2=R_3=Me (*R*)
3b R_1=H, R_2=R_3=Me (*S*)

4a R=H (*R*)
4b R=H (*S*)
5a R=Me (*R*)
5b R=Me (*S*)

We wish to report here a new, efficient method for the preparation of 2-[(coumarin-7-yl)-oxy]propanals **4** and **5**, key intermediates for the synthesis of optically active geiparvarin analogues **2** and **3**.

The preparation of optically active 2-aryloxypropanals may be approached in two distinct ways, viz. the asymmetric hydroformylation of aryl vinyl ethers[4] or the elaboration of functional groups as alcohols,[5] esters,[6] amides[7] and acetals[8] that have no practical application due to the difficulty of their preparation.

Keywords: Enantiopure 2-coumarinyloxypropanals; Geiparvarin analogues; Antitumoral compounds.
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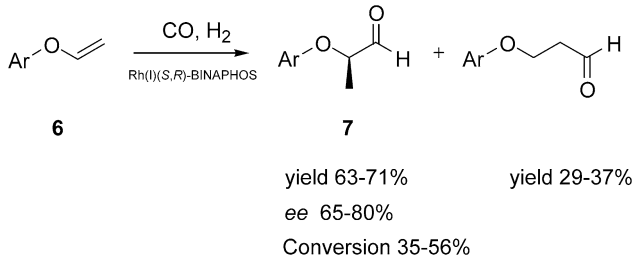


Scheme 1. Hydroformylation of aryl vinyl ethers.

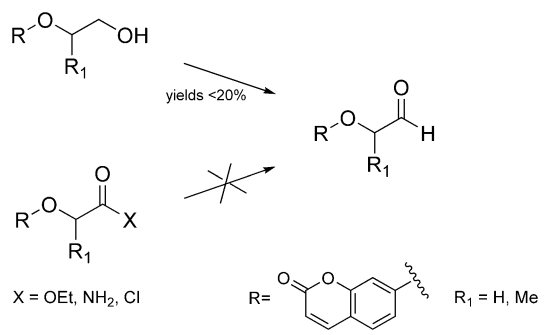
Although abundant work has been published on the hydroformylation of aryl vinyl ethers, few enantioselective examples are reported. Among the more interesting ones, we found a paper by Solinas[4] (Scheme 1) on the hydroformylation of aryl vinyl ethers **6** affording branched 2-aryloxypropanals **7** with 63–70% regioselectivity and 80% of enantiomeric excess but with low conversion (50%).

As reported,[4] if the reaction was allowed to proceed until conversion reached 99% the yield in the branched aldehyde **7** was higher but the enantioselectivity became very poor (30%). On the other hand, while it is easy to obtain enantiopure alcohols, esters or amides, their conversion to the corresponding aldehydes can be problematic. In our hands, the oxidation of 2-hydroxyethoxycoumarins provided 2-oxoethoxycoumarins in no more than 20% yield, while the chemical reduction with $NaBH_4$ or $LiAlH_4$ of the ester, amide or acyl halide failed to give the corresponding aldehyde (Scheme 2).

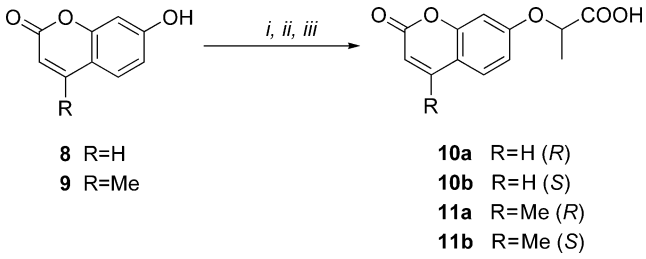
Furthermore, the reaction of coumarin **8** with 2-chloro-1,1-dimethoxypropane[8] did give aldehyde **4** but in the racemic form.

A few years ago, we described[9] the facile and convenient synthesis of 7-(2-oxoethoxy)coumarins from coumarin-7-yloxyacetic acids in excellent overall yields (~97%) starting from the easily available 7-hydroxycoumarins **8** or **9**. On this basis, we now prepared the new enantiopure acids **10** and **11**[10] (Scheme 3).

Application of our methodology to the synthesis of 2-[(coumarin-7-yl)-oxy]propanals **4** and **5** pointed out that the temperature is a most important factor in the reduction of the acyl chloride; if the reaction temperature is kept near the lowest value at which hydrogen chloride starts to evolve, the aldehyde is obtained in very good yields. Attempts to reduce the acyl chloride **12** at higher temperatures, led to a mixture of the aldehyde, 7-hydroxycoumarin, 7-vinyloxycoumarin and 7-ethoxycoumarin as shown in Scheme 4.[11]



Scheme 2. Oxidations and reductions of coumarin derivatives.



Scheme 3. Reagents and conditions: (i) ethyl (2*S*)-hydroxypropanoate or isobutyl (2*R*)-hydroxypropanoate, PPh_3, DIAD, THF, rt; (ii) NaOH 1.25 M, MeOH, rt; (iii) HCl 2.4 M.

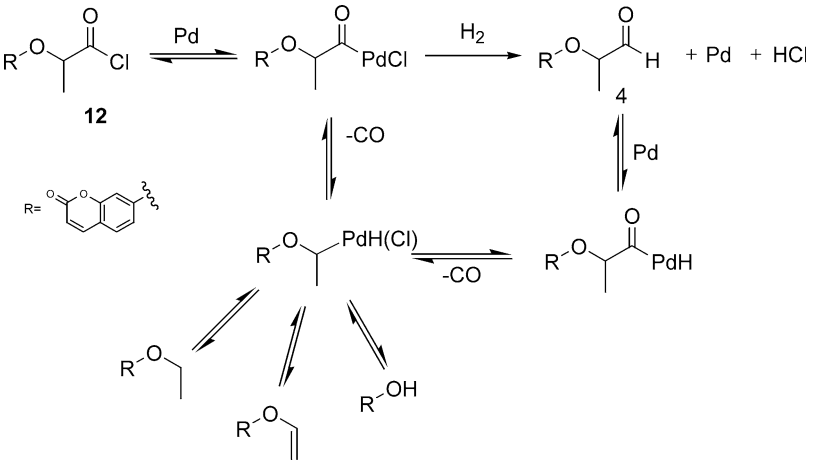
Thus, good overall yields (80–90%) of enantiopure aldehydes can be achieved by the classical Rosenmund reduction of the corresponding acyl chlorides,[12] avoiding the drawback of enantioselective hydroformylation of aryl vinyl ethers. In particular, we point out that the reduction must be performed at a temperature close to 125 °C (no reaction took place below 110 °C) and in the absence of impurities such as thionyl chloride.

After acids **10** and **11** were converted into the corresponding acyl chlorides, subsequent reduction in the above conditions afforded aldehydes **4** and **5**[13] in good yields (Scheme 5).

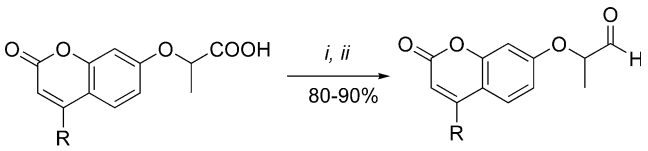
The enantiomeric purity of the aldehydes **4** and **5** was determined by NMR spectroscopy[14] as follows: compound **4a** was converted into the corresponding Schiff's base by reaction with (*R*)-α-methylbenzylamine in methanol and the ^1H NMR spectrum was carefully examined. The presence of only one diastereoisomer confirmed the general applicability of Rosenmund reduction for the synthesis of enantiopure aldehydes starting from 2-aryloxy propionic acids. It is interesting to note that the enantiopure aldehyde obtained by this procedure does not racemize during the reaction, contrary to what other authors observed for chiral non-racemic aldehydes obtained by asymmetric hydroformylation of aryloxy ethylenes employing a chiral rhodium complex.[15]

Finally, the geiparvarin analogues **2** and **3**[16] have been obtained in good overall yield (70%) by condensation of the anion of 2,2,5-trimethyl-3(2*H*)-furanone **13**[17] with aldehyde **4** or **5** and subsequent Stork–Kraus dehydration (Scheme 6).

In conclusion, we demonstrated that the Rosenmund reduction of (*R*)- or (*S*)-2-[(coumarin-7-yl)-oxy]propanoyl chlorides opens a novel path for the synthesis of the corresponding enantiomerically pure aldehydes. These are key intermediates for the synthesis of a new class of geiparvarin analogues.



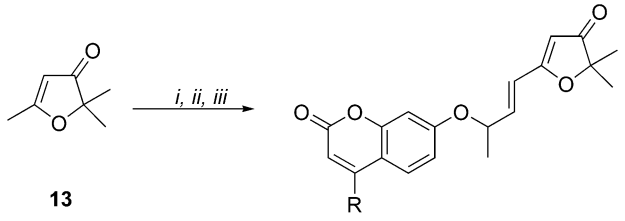
Scheme 4. Catalytic hydrogenation of **12**.



10a R=H (*R*)
10b R=H (*S*)
11a R=Me (*R*)
11b R=Me (*S*)

4a R=H (*R*)
4b R=H (*S*)
5a R=Me (*R*)
5b R=Me (*S*)

Scheme 5. Reagents and conditions: (i) $SOCl_2$, $CHCl_3$; (ii) H_2, Pd/$BaSO_4$, toluene.



2a R=H (*R*)
2a R=H (*S*)
3a R=Me (*R*)
3b R=Me (*S*)

Scheme 6. Reagents and conditions: (i) LDA, THF, −78 °C. (ii) **4** or **5**, THF; (iii) $MeSO_2Cl$, Et_3N, THF, 0 °C.

Acknowledgements

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13. (2*R*)-[(4-Methyl-2-oxo-2*H*-chromen-7-yl)oxy]propanal (**5a**): A mixture of acid **11a** (1 mmol) and thionyl chloride (0.5 mL, 7 mmol) was refluxed for 2 h in dry chloroform (25 mL). Excess of thionyl chloride and chloroform are then removed under reduced pressure to obtain the pure acyl chloride (quantitative yield). Anhydrous toluene (10 mL) and 5% palladium–barium sulfate catalyst (0.050 g) were placed in a round-bottomed flask equipped with a reflux condenser and a gas inlet tube. A slow stream of hydrogen was passed through the stirred mixture while the temperature was raised to 125 °C for 30 min. After cooling to room temperature, the acyl chloride (1 mmol) was added. The mixture was then kept at 125 °C for 3 h under hydrogen flow. After the reaction had cooled to room temperature, the suspension was diluted with ethyl acetate and filtered on Celite to remove the catalyst. Removal of the solvent gave a crude product that was purified by flash chromatography (petroleum ether/ethyl

acetate = 1:1, as an eluant) to afford **5a** as waxy solid (90%): $[\alpha]_D^{20}$ +57.4 (*c* 0.87, $CHCl_3$); IR (CH_2Cl_2) 1735, 1614, 1389 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (d, 1H, $^3J = 1.6$ Hz, H-1′), 7.565 (d, 1H, $^3J = 8.8$ Hz, H-5), 6.91 (dd, 1H, $^3J = 8.8$ Hz and $^4J = 2.5$ Hz, H-6), 6.83 (d, 1H, $^4J = 2.5$ Hz, H-8), 6.20 (d, 1H, $^4J = 1.3$ Hz, H-3), 4.78 (qd, 1H, $^3J = 6.8$ Hz and $^4J = 1.6$ Hz, H-2′), 2.44 (d, 3H, $^4J = 1.3$ Hz, 4-Me), 1.58 (d, 3H, $^3J = 6.8$ Hz, 2′-Me); ^{13}C NMR (100.58 MHz, $CDCl_3$) δ 200.7 (C-1′), 161.3 (C-2), 160.4 (C-7), 155.5 (C-8a), 152.7 (C-4), 126.4 (C-5), 114.9 (C-4a), 113.0 (C-3), 112.9 (C-6), 103.8 (C-8), 78.5 (C-2′), 19.2 (4-Me), 15.8 (2′-Me); MS (EI) *m*/*z* (%): 232 (35, M^+), 203 (100), 175 (20), 159 (12), 91 (37). Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.56; H, 4.92.

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16. Data of 7-{[(1*R*,2*E*)-3-(5,5-dimethyl-4-oxo-4,5-dihydro-2-furanyl)-1-methyl-2-propenyl]oxy}-4-methyl-2*H*-chromen-2-one (**3a**): white waxy solid; $[\alpha]_D^{20}$ +272.1 (*c* 1.07, $CHCl_3$); IR (CH_2Cl_2) 1731, 1702, 1643, 1555, 1278, 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, 1H, $^3J = 7.9$ Hz, H-5) 6.88 (dd, 1H, $^3J = 7.9$ Hz and $^4J = 2.7$ Hz, H-6), 6.80 (d, 1H, $^4J = 2.7$ Hz, H-8), 6.785 (dd, 1H, $^3J = 16.1$ Hz and $^3J = 4.4$ Hz, H-2′), 6.435 (dd, 1H, $^3J = 16.1$ Hz and $^4J = 1.5$ Hz, H-3′), 6.15 (q, 1H, $^4J = 1.2$ Hz, H-3), 5.47 (s, 1H, H-3″), 5.06 (qdd, 1H, $^3J = 6.4$ Hz and $^3J = 4.4$ Hz and $^4J = 1.5$ Hz, H-1′), 2.40 (d, 3H, $^4J = 1.2$ Hz, 4-Me), 1.57 (d, 3H, $^3J = 6.4$ Hz, 1′-Me), 1.40 (s, 6H, 5″-Me); ^{13}C NMR (100.58 MHz, $CDCl_3$) δ 206.0 (C-4″), 180.0 (C-2″), 161.1 (C-2), 160.4 (C-7), 155.2 (C-8a), 152.4 (C-4), 140.4 (C-2′), 125.8 (C-5), 119.6 (C-3′), 114.1 (C-4a), 113.3 (C-6), 112.3 (C-3), 102.6 (C-8), 102.5 (C-3″), 88.6 (C-5″), 73.6 (C-3′), 23.1 (5″-Me), 20.8 (1′-Me), 18.7 (4-Me); MS (EI) *m*/*z* (%): 340 (12, M^+), 176 (17), 165 (71), 91 (15), 77 (53), 69 (100). Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.23; H, 6.23. The (*S*)-enantiomer **3b** has $[\alpha]_D^{20}$ −272.0 (*c* 1.08, $CHCl_3$).
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