# A Short Asymmetric Synthesis of Both Enantiomers of Ramulosin and Its Analogues

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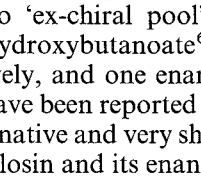
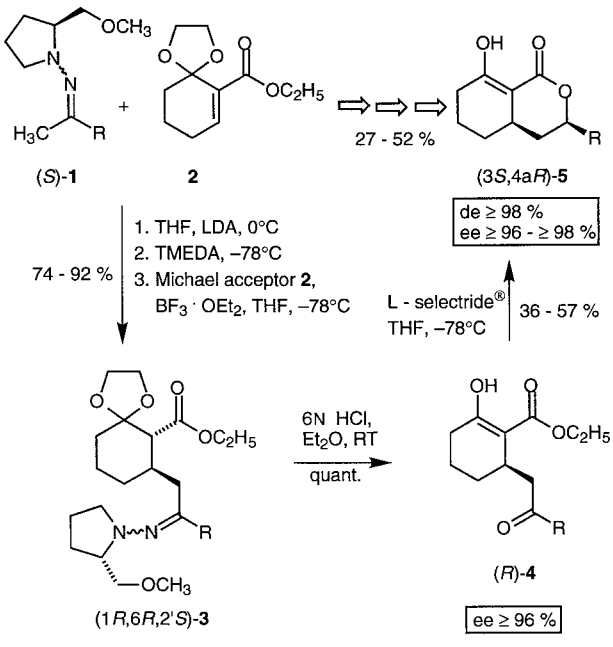
(+)-Ramulosin, a metabolite of *Pestalotia ramulosa*, and its enantiomer have been synthesized in high enantiomeric purity (ee ≥ 98%) via Michael addition of metalated acetone SAMP-hydrazone (*S*)-**1a** to the acetal protected cyclic enoate **2** and subsequent diastereoselective reductive lactonization with L-Selectride. 3-Substituted hexahydroisocoumarines (3*S*,4a*R*)-**5**, analogues of ramulosin, were also obtained with excellent stereoselectivities (de ≥ 98%, ee ≥ 96%) using this method.

(+)-Ramulosin was first isolated from the fungus *Pestalotia ramulosa* by Stodola et al. in the early sixties and inhibits the germination of seeds and spores of microorganisms.[1,2] It is the simplest member of a class of biogenetically related δ-lactone antibiotics. The (3*R*,4a*S*)-configuration of (+)-ramulosin was proposed by Tanenbaum et al.[3] and by Findlay et al.[4] Three syntheses of the racemate,[5] two 'ex-chiral pool' syntheses starting from ethyl (*R*)-3-hydroxybutanoate[6] and (*R*)-*O*-benzylglycidol,[7] respectively, and one enantioselective synthesis[8] of ramulosin have been reported so far. We now wish to describe an alternative and very short asymmetric synthesis of (+)-ramulosin and its enantiomer, as well as of some analogues employing the SAMP/RAMP-hydrazone method.[9]




(+)-*(3R, 4aS)*-ramulosin




| 1,3-5 | a | b | c | d | e |
|---|---|---|---|---|---|
| R | Me | Et | *i*-Pr | *n*-Bu | *i*-Bu |

**Scheme**

As depicted in the Scheme, the methyl ketone SAMP-hydrazones (*S*)-**1**, readily available from the corresponding ketones and (*S*)-1-amino-2-methoxymethyl pyrrolidine (SAMP), were metalated with lithium diisopropylamide in tetrahydrofuran at 0 °C and *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA) was added at − 78 °C to the azaenolate generated. Subsequent reaction with the protected cyclic β-keto enoate **2** in the presence of $BF_3 \cdot OEt_2$ resulted in a clean 1,4-addition and the hydrazone Michael adducts (1*R*,6*R*,2'*S*)-**3** could be obtained in good to excellent yield after purification by distillation (Tables 1 and 4). The acetal protection of the β-carbonyl group of the Michael acceptor **2** turned out to be essential, presumably because of a more favourable γ-deprotonation of the parent β-keto esters by the lithiated hydrazones instead of 1,4-addition and thus resulting in the isolation of only starting material after aqueous workup. Furthermore, to achieve conjugate addition the activation of the Michael acceptor with $BF_3 \cdot OEt_2$ was also essential.

For removal of the chiral auxiliary and the acetal protecting group the crude hydrazones **3** were dissolved in diethyl ether and treated with 6N HCl to effect acidic hydrolysis. The 6-substituted 2-hydroxycyclohex-1-enecarboxylates (*R*)-**4** were obtained in practically quantitative yields as a mixture of keto/enol tautomers (NMR) and with excellent enantiomeric excess (ee ≥ 96%) (Tables 2 and 5). In the final step of our total synthesis of ramulosin and related 3-substituted 8-hydroxyhexahydroisocoumarines (3*S*,4a*R*)-**5**, the keto esters (*R*)-**4** were diastereoselectively reduced with L-Selectride in tetrahydrofuran at − 78 °C which, after aqueous quench, caused directly lactonization. (−)-Ramulosin [(3*S*,4a*R*)-**5a**] and its analogues **5b–e** were obtained in moderate yield, but with excellent diastereomeric (de ≥ 98%) and enantiomeric excess (ee ≥ 96– ≥ 98%) (Tables 3 and 6). For the total synthesis of the naturally occuring (+)-ramulosin RAMP had to be used instead of SAMP as chiral auxiliary. The analytical and spectroscopic data were identical with those reported in the literature (Table 3, footnotes).

The enantiomeric excesses of (*R*)-**4** and (3*S*,4a*R*)-**5** were determined by $^1H$ NMR shift experiments with the chiral cosolvent (−)-(*R*)-9-anthryl-2,2,2-trifluoroethanol or more accurately in the case of **5a** and **5b** by GC analysis on a chiral stationary phase [heptakis(2,3,6-tri-*O*-meth-

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**Table 1.** SAMP-Hydrazones **3** Prepared by 1,4-Addition

| Product | R | Yield (%) | $[\alpha]_D^{r.t.}$ (*c*, $CHCl_3$) |
|---|---|---|---|
| (1*R*, 6*R*, 2′*S*)-**3a** | Me | 90 | + 86.39 (1.47) |
| (1*R*, 6*R*, 2′*S*)-**3b** | Et | 92 | + 67.33 (1.01) |
| (1*R*, 6*R*, 2′*S*)-**3c** | *i*-Pr | 74 | + 43.31 (1.57) |
| (1*R*, 6*R*, 2′*S*)-**3d** | Bu | 81 | + 79.5 (1.61) |
| (1*R*, 6*R*, 2′*S*)-**3e** | *i*-Bu | 80 | + 46.81 (0.94) |

**Table 2.** 6-Substituted 2-Hydroxycyclohex-1-enecarboxylates (*R*)-**4**

| Product | R | Yield (%) | $[\alpha]_D^{r.t.}$ (*c*, $CHCl_3$) | ee[a] (%) |
|---|---|---|---|---|
| (*R*)-**4a** | Me | 100 | − 8.1 (0.86) | ≥ 96 |
| (*S*)-**4a**[b] | Me | 100 | + 8.8 (0.91) | ≥ 96 |
| (*R*)-**4b** | Et | 100 | − 8.6 (1.16) | ≥ 96 |
| (*R*)-**4c** | *i*-Pr | 96 | − 4.5 (1.10) | ≥ 96 |
| (*R*)-**4d** | Bu | 100 | − 10.3 (0.39) | ≥ 96 |
| (*R*)-**4e** | *i*-Bu | 100 | − 11.9 (1.18) | ≥ 96 |

[a] Determined by $^1H$ NMR shift experiments with (−)-(*R*)-(9-anthryl)-2,2,2-trifluoroethanol.
[b] RAMP was used as auxiliary.

**Table 3.** 3-Substituted 8-Hydroxy-3,4,4a,5,6,7-hexahydroisocoumarines **5**

| Product | R | Yield (%) | mp[a] (°C) | $[\alpha]_D^{r.t.}$ (*c*, EtOH) | de[b] (%) | ee (%) |
|---|---|---|---|---|---|---|
| (3*S*,4a*R*)-**5a** | Me | 55 | 117–118 | − 14.8 (1.01)[c] | ≥ 98 | ≥ 96[d] |
| (3*R*,4a*S*)-**5a**[e] | Me | 39 | 117–118[f] | + 18.2 (0.66)[g] | ≥ 98 | ≥ 98[d] |
| (3*S*,4a*R*)-**5b** | Et | 36 | 87–88 | − 14.3 (0.63) | ≥ 98 | ≥ 96[d] |
| (3*R*,4a*R*)-**5c** | *i*-Pr | 51 | 98–99 | − 13.6 (0.22) | ≥ 98 | ≥ 96[h] |
| (3*S*,4a*R*)-**5d** | *n*-Bu | 47 | 98 | − 24.1 (0.29) | ≥ 98 | ≥ 96[h] |
| (3*S*,4a*R*)-**5e** | *i*-Bu | 57 | 101 | − 9.5 (0.21) | ≥ 98 | ≥ 96[h] |

[a] Uncorrected, measured on a Büchi apparatus (Dr. Tottoli).
[b] Determined by $^1H$ and $^{13}C$ NMR spectroscopy.
[c] Relatively large deviation, reason not clear.
[d] Determined by GC analysis on a chiral stationary phase.
[e] RAMP was used as chiral auxiliary.
[f] Ref[8] mp 118–119 °C, ref[6] 118–119 °C; ref[1] 120–121 °C and ref[7] 121–122 °C.
[g] Ref[8] $[\alpha]_D^{22}$ 17.1 (*c* = 0.56, EtOH); ref.[6] $[\alpha]_D^{22}$ 18.2 (*c* = 1.15, EtOH); ref[1] $[\alpha]_D^{25}$ 18 ± 2 (*c* = 2.90, EtOH); ref[7] $[\alpha]_D^{26}$ 18.1 (*c* = 1.03, EtOH).
[h] Determined by $^1H$ NMR shift experiments with (−)-(*R*)-(9-anthryl)-2,2,2-trifluoroethanol.

yl)-β-cyclodextrin in OV 1701]. The racemic keto esters **4** required for comparison were prepared via the corresponding dimethylhydrazone homocuprates according to the method previously described.[10] The de values of the final products **5** were determined by $^1H$ and $^{13}C$ NMR spectroscopy.

The assignment of the relative and absolute configurations presented in the Scheme are not only based on the polarimetric data of **5a**, but also on the unambiguously assigned configuration (X-ray structure analysis) of related compounds prepared by MIRC reactions.[11] The (*R*)-configuration of the stereogenic center generated in the first step of the asymmetric Michael addition is in agreement with previous results of 1,4-additions via metalated SAMP-hydrazones[12] and the postulated mechanism of electrophilic substitutions with SAMP/RAMP-hydrazones.[9]

Another possibility to synthesize the hydrazones (1*R*,6*R*,2′*S*)-**3** is by using a Michael initiated ring closure (MIRC) reaction of metalated SAMP-hydrazones with ethyl 6-ethoxycarbonylhex-2-enoate, but this procedure gave lower yields of hydrazones **3**.[13]

In summary, a very short, highly diastereo- and enantioselective synthesis of (+)-ramulosin and its enantiomer employing the SAMP/RAMP-hydrazone method has been developed. Key steps of the synthesis are the Michael addition of metalated methyl ketone SAMP-hydrazones to the protected cyclic enoate **2** and the diastereoselective reductive lactonization with L-Selectride. The new method offers an efficient entry to a variety of 3-substituted hexahydroisocoumarines and 6-substituted 2-hydroxycyclohex-1-enecarboxylates[14] with high asymmetric induction, both valuable classes of compounds in natural product synthesis.

Solvents were dried and purified according to literature procedures prior to use. All reagents were of commercial quality from freshly opened containers or distilled before use. THF was freshly distilled from potassium under argon. Light petroleum refers to the fraction with bp 40–80 °C. Analytical TLC plates (silica gel 60 $F_{254}$) and silica gel 60 (230–400 mesh) were purchased from Merck, Darmstadt. *n*-BuLi (1.6 N in *n*-hexane) and L-Selectride was purchased from Aldrich. All melting points (Büchi apparatus, system Dr. Tottoli) are uncorrected. Optical rotation values were measured using a Perkin-Elmer P 241 polarimeter. Microanalyses were obtained with a Heraeus CHN–O-RAPID element analyzer. MS were recorded on a Varian MAT 212 (70 eV, 1 mA) spectrometer with DEI ionisation. IR spectra were obtained using a Perkin-Elmer FT 1750 spectrometer. The $^1H$ and $^{13}C$ NMR spectra were measured on a Varian VXR 300 (300 and 75 MHz) and Gemini 300 (300 and 75 MHz) using TMS as internal standard. (S)-1-amino-2-methoxymethylpyrrolidine (SAMP), (*R*)-1-amino-2-methoxymethylpyrrolidine (RAMP),[15] the ketone SAMP/RAMP-hydrazones and the Michael acceptor[16] were synthesized according to literature procedures.

**Ethyl (1*R*,6*R*)-2,2-(Ethylenedioxy)-6-[2-[[2′*S*)-2′-(methoxymethyl)-pyrrolidino]imino]alkyl]cyclohexanecarboxylate; SAMP-Hydrazone (1*R*,6*R*,2′*S*)-3; General Procedure:**

A solution of 1.6 M BuLi in hexane (2.2 equiv) was added dropwise to a solution of *i*-$Pr_2NH$ (2.2 equiv) in THF (typically 10 mL/mmol) under Ar at 0 °C. The mixture was stirred to generate a clear and colorless solution of LDA (2.2 equiv). After dropwise addition of SAMP- or RAMP-hydrazone (*S*)- or (*R*)-**1** (1.8 equiv) the mixture was stirred for 4 h to obtain a colored solution or suspension of the nucleophile. The mixture was subsequently cooled to − 78 °C and TMEDA (5 equiv) was added. Stirring was continued for an additional 0.5 h. Then a solution of the Michael acceptor **2** (1 equiv) and $BF_3 \cdot OEt_2$ (1 equiv) in THF (5 mL) was added. The reaction mixture was stirred ca. 12 h at − 78 °C. After addition of sat. $NH_4Cl$ (10 mL), the reaction mixture was stirred 20 min at r.t. Then water (10 mL) and $Et_2O$ (50 mL) were added and the phases were separated. The aqueous phase was extracted with $Et_2O$ (2 × 50 mL). The collected organic phases were washed with brine (10 mL), dried ($MgSO_4$), concentrated in vacuo and the residue was purified by distillation.

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**Table 4.** Spectroscopic Data of the SAMP Hydrazones **3**[a]

| Compound | IR ($CHCl_3$) $\nu$ ($cm^{-1}$) | $^1H$ NMR ($CDCl_3$/TMS) $\delta$, $J$ (Hz) | $^{13}C$ NMR ($CDCl_3$/TMS) $\delta$ | MS (70 eV) $m/z$ (%) |
|---|---|---|---|---|
| **3a** | 2940, 2870, 1730, 1680, 1674, 1448, 1369, 1245, 1203, 1181, 1097, 1059, 1034 | 1.30 (t, $J$ = 7.0, 3H, $CH_2CH_3$), 1.40–2.40 [m, 17H, $CH_2CH_2CH_2C(O)_2$, $CH_2CN$, $CHCH_2CN$, $CHCO_2$, $NCH_2CH_2$, $CH_3$], 3.34 (s, 3H, $OCH_3$), 2.9–3.5 (m, 6H, $OCH_2CH_2O$,$NCH_2$), 3.6–3.85 (m, 2H, NCH, CHHO), 3.98 (m, 1H, CHHO), 4.2 (q, $J$ = 7.1, 2H, $CH_2CH_3$) | 14.3 ($CH_2CH_3$), 17.7 ($CH_3$), 21.6 ($NCH_2CH_2$), 26.4 ($NCHCH_2$), 27.1 ($CH_2CH$), 31.7 ($CHCH_2CN$), 31.8, 34.5, 36.0 [$CH_2CH_2C(O)_2$, $CH_2CN$], 54.8 ($NCH_2$), 59.0 ($OCH_3$), 59.2 ($CHCO_2$), 60.9 ($CH_2CH_3$), 65.6, 66.1 ($OCH_2CH_2O$), 68.1 (NCH), 75.6 ($CH_2O$), 107.1 [$C(O)_2$], 162.8 ($CN$), 167.7 ($CO_2$) | 383 ($M^{+\cdot}$ + 1, 0.3), 382 ($M^{+\cdot}$, 1), 337 (12), 197 (17), 123 (100), 111 (10), 87 (17), 83 (11), 73 (100), 70 (35), 61 (61), 60 (12) |
| **3b** | 2940, 2864, 1697, 1630, 1460, 1448, 1371, 1244, 1216, 1181, 1107, 1057, 926, 666, 534, 475 | 0.9 (t, $J$ = 7.4, 3H, $CNCH_2CH_3$), 1.3 (t, $J$ = 7.0, 3H, $CH_2CH_3$), 1.0–2.5 [m, 16H, $CH_2CH_2CH_2C(O)_2$, $CH_2CN$, $CHCH_2CN$, $CHCO_2$, $NCH_2CH_2CH_2$, $CNCH_2CH_3$], 3.33 (s, 3H, $OCH_3$), 2.9–3.45 (m, 6H, $OCH_2CH_2O$, $NCH_2$), 3.7–3.84 (m, 2H, NCH, CHHO), 3.98 (m, 1H, CHHO), 4.23 (q, $J$ = 7.0, 2H, $CH_2CH_3$) | 12.2 ($CNCH_2CH_3$), 14.3 ($CH_2CH_3$), 22.1 ($CNCH_2CH_3$), 25.3 ($NCH_2CH_2$), 26.7 ($NCHCH_2$), 27.2 ($CH_2CH$), 31.6 ($CHCH_2CN$), 32.2 [$CH_2CH_2C(O)_2$], 33.5 [$CH_2CH_2C(O)_2$], 35.1 ($CH_2CN$), 54.8 ($NCH_2$), 58.9 ($CHCO_2$), 59.2 ($OCH_3$), 60.9 ($CH_2CH_3$), 65.6, 65.7 ($OCH_2CH_2O$), 66.1 (NCH), 75.6 ($CH_2O$), 108.6 [$C(O)_2$], 163.4 ($CN$), 167.6 ($CO_2$) | 397 ($M^{+\cdot}$ + 1, 6), 396 ($M^{+\cdot}$, 22), 359 (10), 352 (22), 351 (100), 305 (10), 184 (17), 183 (33), 167 (19), 139 (14), 137 (14), 124 (24), 114 (23), 99 (11), 70 (31), 57 (11), 55 (16), 45 (34), 43 (91) |
| **3c**[b] | 2977, 2939, 2873, 1692, 1447, 1379, 1347, 1324, 1174, 1125, 1099, 950, 846 | 1.09 [d, $J$ = 7.1, 3H, $CH(CH_3)_2$], 1.12 [d, $J$ = 6.7, 3H, $CH(CH_3)_2$], 1.31 (t, $J$ = 7.4, 3H, $CH_2CH_3$), 1.56–2.4 [m, 14H, $CH_2CH_2CH_2C(O)_2$, $CH_2CN$, $CHC_2CN$, $CHCO_2$, $NCH_2CH_2CH_2$], 2.56, 2.58 [q, $J$ = 6.7, q, $J$ = 7.1, 1H, $CH(CH_3)_2$], 2.9–3.45 (m, 6H, $OCH_2CH_2O$, $NCH_2$), 3.33 (s, 3H, $OCH_3$), 3.7–3.88 (m, 2H, NCH, CHHO), 4.0 (m, 1H, CHHO), 4.23 (q, $J$ = 7.1, 2H, $CH_2CH_3$) | 14.3 ($CH_2CH_3$), 19.5 [$CH(CH_3)_2$], 21.9 ($NCH_2CH_2$), 22.1 [$CH(CH_3)_2$], 26.5 ($NCHCH_2$), 27.1 ($CH_2CH$), 31.1 [$CH_2CH_2C(O)_2$], 32.0, 32.2, 33.6 [$CH_2CH_2C(O)_2$], 32.0, 32.2, 33.6 [$CH_2CH_2C(O)_2$, $CHCH_2CN$, $CH_2CN$], 54.5 ($NCH_2$), 58.9 ($OCH_3$), 59.1 ($CHCO_2$), 60.9 ($CH_2CH_3$), 65.7 (NCH), 66.1, 68.1 ($OCH_2CH_2O$), 76.2 ($CH_2O$), 113.6 [$C(O)_2$], 163.3 ($CN$), 167.7 ($CO_2$) | 411 ($M^{+\cdot}$ + 1, 5), 410 ($M^{+\cdot}$, 18), 366 (22), 365 (100), 319 (27), 208 (17), 206 (12), 167 (16), 164 (16), 153 (15), 137 (11), 123 (23), 114 (19), 70 (33), 55 (15), 45 (23), 43 (17), 42 (20), 41 (14) |
| **3d**[b] | 2970, 2930, 2860, 1700, 1445, 1375, 1320, 1245, 1120, 1095, 1045, 950, 880, 845, 800 | 0.92 [t, $J$ = 7.0, 3H, $(CH_2)_3CH_3$], 1.3 (m, 7H, $CH_2CH_2CH_2CH_3$, $CH_2CH_3$), 1.40–2.60 [m, 15H, $CH_2CH_2CH_2C(O)_2$, $CH_2CO_2$, $CH_2CN$, $NCH_2CH_2CH_2$, 2.9–3.5 (m, 7H, $OCH_2CH_2O$, $NCH_2$, $CHCH_2CN$), 3.7–3.85 (m, 2H, NCH, CHHO), 3.99 (m, 1H, CHHO), 4.23 (q, $J$ = 7.1, 2H, $CH_2CH_3$) | 13.9 [$(CH_2)_3CH_3$], 14.3 ($CH_2CH_3$), 22.6 ($NCH_2CH_2$), 22.9 [$(CH_2)_2CH_2CH_3$], 26.6 ($NCHCH_2$), 27.1 ($CH_2CH$), 29.8 ($CH_2CH_2C_2H_5$), 31.7 ($CHCH_2CN$), 33.7 [$CH_2CH_2C(O)_2$], 34.6 [$CH_2CH_2C(O)_2$], 34.9 ($CH_2C_3H_7$), 40.1 ($CH_2CN$), 54.8 ($NCH_2$), 59.0 ($OCH_3$), 60.3 ($CHCO_2$), 60.9 ($CH_2CH_3$), 65.9 (NCH), 65.6, 68.1 ($OCH_2CH_2O$), 75.6 ($CH_2O$), 113.6 [$C(O)_2$], 163.5 ($CN$), 167.6 ($CO_2$) | 425 ($M^{+\cdot}$ + 1, 5), 424 ($M^{+\cdot}$, 17), 380 (26), 379 (100), 333 (12), 211 (13), 167 (16), 123 (13), 114 (17), 70 (18), 57 (13), 45 (13), 43 (20), 41 (13) |
| **3e**[c] | 2978, 2940, 2873, 1700, 1447, 1379, 1347, 1424, 1297, 1262, 1172, 1125, 1098, 1049, 949, 847 | 0.85 [d, $J$ = 6.4, 3H, $CH_2CH(CH_3)_2$], 0.92 (t, $J$ = 6.4, 3H, $CH_2CH_3$), 0.98 [d, $J$ = 6.4, 3H, $CH(CH_3)_2$], 1.26–2.42 [m, 17H, $CH_2CH_2CH_2C(O)_2$, $CH_2CN$, $CHCH_2CN$, $CHCO_2$, $NCH_2CH_2CH_2$, $CH_2CH(CH_3)_2$], 3.34 (s, 3H, $OCH_3$), 2.98–3.44 (m, 6H, $OCH_2CH_2O$, $NCH_2$), 3.75–3.92 (m, 2H, NCH, CHHO), 4.0 (m, 1H, CHHO), 4.21 (q, $J$ = 7.1, 2H, $CH_2CH_3$) | 14.2 ($CH_2CH_3$), 21.9 ($NCH_2CH_2$), 22.1, 22.2 [$CH(CH_3)_2$], 25.8 [$CH(CH_3)_2$], 26.3 ($NCHCH_2$), 27.1 ($CH_2CH$), 31.7 ($CHCH_2CN$), 33.6 [$CH_2CH_2C(O)_2$], 34.0 [$CH_2CH_2C(O)_2$], 35.7 ($CH_2CN$), 45.2 [$CH_2CH(CH_3)_2$], 54.8 ($NCH_2$), 59.0 ($OCH_3$), 59.2 ($CHCO_2$), 60.9 ($CH_2CH_3$), 65.6, 66.1 ($OCH_2CH_2O$), 65.9 (NCH), 75.5 ($CH_2OCH_3$), 104.3 [$C(O)_2$], 163.5 ($CN$), 167.6 ($CO_2$) | 425 ($M^{+\cdot}$ + 1, 4), 424 ($M^{+\cdot}$, 16), 380 (26), 370 (100), 333 (18), 220 (11), 212 (12), 211 (15), 181 (12), 167 (29), 137 (16), 123 (36), 114 (40), 99 (12), 95 (13), 70 (59), 57 (30), 55 (23), 45 (45), 43 (35), 41 (38) |

[a] Satisfactory HRMS obtained for **3a–e**. The NMR data are those of the major geometric isomer.
[b] IR spectrum determined in $Et_2O$.
[c] IR spectrum determined as film.

**6-Substituted 2-Hydroxycyclohex-1-enecarboxylates (*R*)-4; General Procedure:**

The crude or purified hydrazone **3** was dissolved in $Et_2O$ (10 mL), then 6N HCL (5 mL) was added. After stirring at r.t. for 30 min, $Et_2O$ (50 mL) was added and the phases were separated. The aqueous phase was extracted with $Et_2O$ (2 × 50 mL). The collected organic phases were washed with pH 7 buffer and water, dried ($MgSO_4$), concentrated in vacuo, and the residue was purified by flash column chromatography (silica gel, light petroleum/$Et_2O$ 1 : 1).

**3-Substituted 8-Hydroxy-3,4,4a,5,6,7-hexahydroisocoumarines (3*S*,4a*R*)-5; General Procedure:**

L-Selectride (2 equiv) was added dropwise to a solution of the purified cyclohexenecarboxylate **4** in THF under Ar at −78 °C. Stirring was continued for 1 h. Then the reaction mixture was quenched with water (2 mL) at −78 °C and stirring was continued until the reaction mixture reached r.t. After addition of $Et_2O$ (20 mL), the phases were separated. The organic phase was washed with brine, dried ($MgSO_4$), concentrated in vacuo and was purified by flash column chromatography (silica gel, light petroleum/$Et_2O$).

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**Table 5.** Spectroscopic Data of the 6-Substituted 2-Hydroxycyclohex-1-enecarboxylates (*R*)-**4**[a]

| Compound | IR (KBr) $\nu$ ($cm^{-1}$) | $^1H$ NMR ($CDCl_3$/TMS) $\delta$, $J$ (Hz) | $^{13}C$ NMR ($CDCl_3$/TMS) $\delta$ | MS (70 eV) *m/z* (%) |
|---|---|---|---|---|
| **4a** | 2980, 2940, 2871, 1740, 1714, 1646, 1613, 1423, 1403, 1368, 1288, 1257, 1224, 1179, 1164, 1148 | 1.28 (t, $J$ = 7.0, 3H, $CH_2CH_3$), 1.40–1.80 (m, 4H, $CH_2CH_2CH$, $CH_2CH_2CO$), 1.80–2.10 (m, 1H, CHCHH), 2.20–2.74 (m, 4H, $CH_2CO$, CHCHH, $CHCH_2$), 2.14 (s, 3H, $COCH_3$), 3.09–3.16 (m, $CHCO_2$, keto), 4.22 (q, $J$ = 7.0, 2H, $CH_2CH_3$), 12.43 (s, OH, enol) | 14.2 ($CH_2CH_3$), 26.4 ($CH_2CH_2CH$), 29.4 ($CH_2CH$), 30.4 ($COCH_3$), 36.9 ($CHCH_2$), 41.1 [$CH_2C(OH)$], 48.6 ($CH_2CO$), 61.2 ($CH_2CH_3$), 62.4 (CHCO, keto), 100.9 (C = C(OH), enol), 173.5 ($CO_2$), 205.4 ($COCH_3$), 206.5 (COH), 208.3 (C=O) | 226 ($M^{+\bullet}$, 4), 180 (21), 169 (25), 165 (26), 137 (11), 124 (15), 123 (50), 95 (15), 55 (16), 45 (13), 44 (18), 43 (100), 41 (15), 39 (10) |
| **4b** | 2978, 2940, 2877, 1742, 1713, 1646, 1613, 1460, 1421, 1402, 1365, 1289, 1257, 1224, 1210, 1180, 1074 | 1.06 (t, $J$ = 7.1, 3H, $COCH_2CH_3$), 1.29 (t, $J$ = 7.0. 3H, $CH_2CH_3$), 1.46–1.78 (m, 4H, $CH_2CH_2CH$, $CH_2CH_2CO$), 1.96–2.09 (m, 1H, CHCHH), 2.23–2.72 (m, 6H, $CH_2CO$, CHCHH, CHCHH, $CHCH_2$, $COCH_2CH_3$), 3.13 (m, $CHCO_2$, keto), 4.22 (q, $J$ = 7.1, 2H, $CH_2CH_3$), 12.44 (s, OH, enol) | 7.9 ($COCH_2CH_3$), 14.2 ($CH_2CH_3$), 26.4 ($CH_2CH_2CH$), 29.1 ($CH_2CH$), 36.1 ($COCH_2CH_3$), 36.9 ($CHCH_2$), 41.1 [$CH_2C(OH)$], 47.1 ($CH_2CO$), 60.4 ($CH_2CH_3$), 62.5 (CHCO, keto), 101.1 [C=C(OH), enol], 173.4 ($CO_2$), 205.5 ($COC_2H_5$), 209.3 (COH), 210.9 (C=O) | 240 ($M^{+\bullet}$, 13), 194 (13), 169 (44), 165 (49), 137 (16), 123 (89), 97 (11), 95 (21), 83 (13), 81 (15), 71 (13), 69 (15), 67 (16), 57 (27), 55 (26), 45 (13), 43 (100) |
| **4c**[b] | 3406, 2970, 2938, 2873, 1741, 1713, 1647, 1613, 1466, 1450, 1402, 1383, 1368, 1286, 1256, 1225, 1211, 1179, 1152, 1078 | 1.09 [d, $J$ = 6.7, 3H, $CH(CH_3)_2$], 1.10 [d, $J$ = 6.7, 3H, $CH(CH_3)_2$], 1.28 (t, $J$ = 7.0, 3H, $CH_2CH_3$), 1.45–1.78 (m, 4H, $CH_2CH_2CH$, $CH_2CH_2CO$), 2.00–2.75 (m, 5H, $CHCH_2CO$, $CH_2CO$, $CHCH_2$), 2.60, 2.61 [q, $J$ = 7.0, q, $J$ = 7.0, 1H, $CH(CH_3)_2$], 3.15 (m, $CHCO_2$, keto), 4.22 (q, $J$ = 7.0, 2H, $CH_2CH_3$), 12.44 (s, OH, enol) | 14.2 ($CH_2CH_3$), 18.3, 18.2 [$CH(CH_3)_2$], 26.4 ($CH_2CH_2CH$), 29.1 ($CH_2CH$), 36.3 ($CHCH_2$), 40.8 [$CH(CH_3)_2$], 41.1 [$CH_2C(OH)$], 44.9 ($CH_2CO$), 60.4 ($CH_2CH_3$), 62.5 (CHCO, keto), 101.1 (C=C(OH), enol), 173.5 ($CO_2$), 205.7 [$COCH(CH_3)_2$], 212.6 (COH), 214.0 (C=O) | 255 ($M^{+\bullet}$ + 1, 254 ($M^{+\bullet}$, 9), 211 (9), 209 (10), 208 (11), 169 (100), 165 (64), 137 (14), 123 (99), 95 (16), 71 (28), 67 (11), 55 (38), 43 (58), 41 (25), 39 (14) |
| **4d** | 3450, 2970, 2930, 2870, 1705, 1445, 1375, 1340, 1320, 1175, 1120, 1095, 1045, 945, 840, 800 | 0.91 [t, $J$ = 7.4, 3H, $(CH_2)_3CH_3$], 1.29 (t, $J$ = 7.0, 3H, $CH_2CH_3$), 1.29 [m, 2H, $(CH_2)_2CH_2CH_3$], 1.48–1.75 (m, 5H, $CH_2CH_2CH$, $CH_2CH_2CO$, CHCHH), 2.03 (m, 1H, $CHCH_2$), 2.2–2.74 (m, 7H, $CH_2CO$, CHCHH, $CH_2C_3H_7$, $CH_2CH_2C_2H_5$), 3.12 (m, $CHCO_2$, keto), 4.22 (q, $J$ = 7.0, 2H, $CH_2CH_3$), 12.43 (s, OH, enol) | 13.9 [$(CH_2)_3CH_3$], 14.2 ($CH_2CH_3$), 22.4 [$(CH_2)_2CH_2CH_3$], 25.8 ($CH_2CH_2C_2H_5$), 26.4 ($CH_2CH_2CH$), 27.6 [$(CH_2)_3CH_3$], 36.9 ($CHCH_2$), 41.1 —$CH_2C(OH)$], 42.7 ($CH_2C_3H_7$), 47.4 ($CH_2CO$), 60.4 ($CH_2CH_3$), 62.5 (CHCO, keto), 101.0 [C=C(OH), enol], 173.4 ($CO_2$), 205.5 ($COC_4H_9$), 208.6 (COH), 210.6 (C=O) | 268 ($M^{+\bullet}$, 10), 222 (13), 169 (84), 168 (14), 166 (16), 165 (76), 137 (18), 124 (14), 123 (100), 122 (11), 95 (21), 94 (17), 85 (39), 81 (10), 79 (10), 67 (11), 57 (53), 55 (48), 45 (12), 43 (55), 41 (45), 39 (18) |
| **4e**[b] | 3405, 2957, 2872, 1742, 1713, 1647, 1613, 1466, 1422, 1403, 1367, 1334, 1285, 1257, 1223, 1180, 1146, 1095, 1080, 1064, 1047 | 0.91 [d, $J$ = 6.6, 3H, $CH(CH_3)_2$], 0.93 [d, $J$ = 6.4, 3H, $CH(CH_3)_2$], 1.29 (t, $J$ = 7.4, 3H, $CH_2CH_3$), 1.50–1.74 (m, 4H, $CH_2CH_2CH$, $CH_2CH_2CO$), 1.98–2.72 [m, 8H, $CH_2CO$, $CHCH_2$, $CHCH_2CO$, $CH_2CH(CH_3)_2$, $CH(CH_3)_2$], 3.08–3.18 (m, $CHCO_2$, keto), 4.22 (q, $J$ = 7.0, 2H, $CH_2CH_3$), 12.52 (s, OH, enol) | 14.3 ($CH_2-CH_3$), 22.5/22.6 [$CH(CH_3)_2$], 24.8 [$CH_2CH(CH_3)_2$], 26.3 ($CH_2CH_2CH$), 29.1 ($CH_2CH$), 36.8 ($CHCH_2$), 41.1 [$CH_2C(OH)$], 47.9 ($CH_2CO$), 51.9 [$CH_2CH(CH_3)_2$], 60.4 ($CH_2CH_3$), 62.5 (CHCO, keto), 100.9 [C=C(OH), enol], 173.5 ($CO_2$), 201.9 ($COC_4H_9$), 208.6 (COH), 210.2 (C=O) | 269 ($M^{+\bullet}$ + 1, 2) 268 ($M^{+\bullet}$, 17), 222 (19), 179 (15), 169 (87), 168 (12), 166 (18), 165 (83), 137 (14), 123 (100), 95 (16), 94 (12), 85 (40), 57 (49), 55 (34) |

[a] Satisfactory microanalyses obtained for **4a–e**: C ± 0.5, H ± 0.23. NMR data of keto and enol form are given.
[b] IR spectrum determined in $CHCl_3$.

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**Table 6.** Spectroscopic Data of the 3-Substituted 8-Hydroxy-3,4,4a,5,6,7-hexahydroisocoumarines (3*S*,4a*R*)-**5**[a]

| Compound | IR (KBr) $\nu$ ($cm^{-1}$) | $^1H$ NMR ($CDCl_3$/TMS) $\delta$, $J$ (Hz) | $^{13}C$ NMR ($CDCl_3$/TMS) $\delta$ | MS (70 eV) $m/z$ (%) |
|---|---|---|---|---|
| **5a**[b] | 3448, 2977, 2927, 2875, 2857, 1642, 1619, 1447, 1407, 1387, 1355, 1305, 1270, 1235, 1200, 1170, 1145, 1105, 1065, 1020, 960, 890 | 1.09–1.34 [m, 2H, $CH_{ax}HCHCH_3$, $CH_{ax}HCH_2CH_2C(OH)=$], 1.38 (d, $J$ = 6.3, 3H, $CH_3$), 1.56–1.74 [m, 1H, $CH_{ax}HCH_2C(OH)=$], 1.84–1.94 [m, 2H, $CH_{eq}CH_2CH_2C(OH)=$, $CH_{eq}CH_2C(OH)=$], 1.95–1.98 (dd, $J$ = 2.4, 3.7, 1H, $CH_{eq}CHCH_3$), 2.34–2.41 [m, 2H, $CH_2C(OH)=$], 2.45–2.58 (m, 1H, $CHCH_2CH$), 4.40–4.52 (ddq, $J$ = 2.4, 12.8, 6.4, 1H, $CHCH_3$), 13.26 (s, 1H, OH) | 20.9 [$CH_2CH_2C(OH)=$], 21.7 ($CH_3$), 29.5, 29.1 [$CH_2CHCH_2$, $CH_2C(OH)=$], 33.0 ($CHCH_2CH$), 37.5 ($CH_2CHOCO$), 76.6 ($CHOCO$), 96.8 ($CCO_2$), 171.8 ($CO_2$), 174.8 [$C(OH)=$] | 183 ($M^{+\cdot}$ + 1, 10), 182 ($M^{+\cdot}$, 71), 154 (39), 141 (28), 139 (17), 136 (29), 126 (55), 123 (100), 121 (17), 112 (15), 96 (12), 95 (14), 84 (14), 79 (11), 68 (12), 67 (17), 55 (37), 43 (19), 41 (24), 39 (20) |
| **5b**[c] | 3364, 2964, 2936, 2867, 1636, 1455, 1412, 1378, 1323, 1300, 1227, 1209, 1196, 1173, 1132, 1104, 1077, 990, 959, 871 | 1.00 (t, $J$ = 7.7, 3H, $CH_3$), 1.09–1.37 [m, 2H, $CH_{ax}HCHC_2H_5$, $CH_{ax}HCH_2CH_2C(OH)=$], 1.58–1.82 [m, 3H, $CH_2CH_3$, $CH_{ax}HCH_2C(OH)=$], 1.85–1.96 [m, 3H, $CH_{eq}CHC_2H_5$, $CH_{eq}CH_2CH_2C(OH)=$, $CH_{eq}CH_2C(OH)=$], 2.38 [m, 2H, $CH_2C(OH)=$], 2.50 (m, 1H, $CHCH_2CH$), 4.25 (m, 1H, $CHC_2H_5$), 13.27 (s, 1H, OH) | 9.2 ($CH_3$), 20.9 [$CH_2CH_2C(OH)=$], 28.7, 29.1, 29.7 [$CH_2CHCH_2$, $CH_2C(OH)=$, $CH_2CH_3$], 32.9 ($CHCH_2CH$), 35.1 ($CH_2CHOCO$), 81.4 ($CHOCO$), 97.2 ($CCO_2$), 171.7 ($CO_2$), 174.6 [$C(OH)=$] | 197 ($M^+$ + 1, 6), 196 ($M^{+\cdot}$, 45), 178 (17), 141 (22), 140 (14), 123 (100), 95 (12), 94 (31), 55 (10) |
| **5c**[c] | 3365, 2973, 2944, 2892, 2872, 1642, 1453, 1417, 1382, 1355, 1323, 1311, 1264, 1254, 1237, 1182, 1166, 1132, 1085, 1001, 947, 881, 840 | 0.98 [d, $J$ = 7.0, 3H, $CH(CH_3)_2$], 1.00 (d, $J$ = 6.7, 3H, $CH(CH_3)_2$], 1.1–1.34 (m, 1H, $CH_{ax}HCHC_3H_7$), 1.58–1.74 [m, 2H, $CH_{ax}HCH_2CH_2C(OH)=$, $CH_{ax}HCH_2C(OH)=$], 1.84–1.98 [m, 4H, $CH_{eq}HCHC_3H_7$, $CH_{eq}HCH_2CH_2C(OH)=$, $CH_{eq}HCH_2C(OH)=$), $CH(CH_3)_2$], 2.37 ]m, 2H, $CH_2C(OH)=$], 2.48 (m, 1H, $CHCH_2CH$), 4.11 (ddd, $J$ = 2.3, 5.0, 5.4, 1H, $CHC_3H_7$), 13.27 (s, 1H, OH) | 17.6, 17.8 [$CH(CH_3)_2$], 20.9 [$CH_2CH_2C(OH)=$], 29.0, 29.7 [$CH_2CHCH_2$, $CH_2C(OH)=$], 32.1 ($CH_2CHOCO$), 32.6 [$CH(CH_3)_2$], 32.9 ($CHCH_2CH$) 84.8 ($CHOCO$), 97.3 ($CCO_2$), 172.0 ($CO_2$), 174.5 [$C(OH)=$] | 211 ($M^{+\cdot}$ + 1, 3), 210 ($M^{+\cdot}$, 16), 141 (26), 125 (14), 123 (100), 108 (47), 95 (11), 93 (11), 55 (24), 43 (29), 41 (19), 39 (13) |
| **5d** | 3433, 2955, 2937, 2862, 1637, 1468, 1457, 1415, 1364, 1330, 1305, 1252, 1241, 1172, 1107, 1045, 1006, 871 | 0.91 (t, $J$ = 7.4, 3H, $CH_3$), 1.08–1.74 [m, 9H, $CH_{ax}HCHC_4H_9$, $CH_{ax}HCH_2CH_2C(OH)=$, $CH_{ax}HCH_2C(OH)=$, $CH_2C_3H_7$, $CH_2CH_2C_2H_5$, $(CH_2)_2CH_2CH_3$], 1.84–1.98 [m, 3H, $CH_{eq}HCHC_4H_9$ | 13.9 [$(CH_2)_3CH_3$], 20.9 [$CH_2CH_2C(OH)=$], 22.5 [$(CXH_2)_2CH_2CH_3$], 26.9 ($CH_2CH_2C_2H_5$), 29.0, 29.6 [$CH_2CHCH_2$, $CH_2C(OH)=$], 32.9 ($CHCH_2CH$), 35.5 ($CH_2C_3H_7$), 35.6 ($CH_2CHOCO$), 80.2 ($CHOCO$), 97.2 ($CCO_2$), 171.9 ($CO_2$), 174.6 [$C(OH)=$] | 225 ($M^{+\cdot}$ + 1, 3), 224 ($M^{+\cdot}$, 20), 206 (9), 141 (37), 123 (100), 122 (30), 95 (11), 79 (9), 67 (8), 55 (19), 43 (24), 41 (14) |
| **5e** | 3360, 2951, 2897, 2872, 1642, 1457, 1412, 1385, 1368, 1306, 1260, 1236, 1171, 1152, 1109, 1067, 1047, 989 | 0.93 [d, $J$ = 6.4, 3H, $CH(CH_3)_2$], 0.94 [d, $J$ = 6.7, 3H, $CH(CH_3)_2$], 1.08–1.39 [m, 2H, $CH_{ax}HCHC_4H_9$, $CH_{ax}HCH_2CH_2C(OH)=$], 1.55–1.73 (m, 3H, $CH_{ax}HCH_2C(OH)=$, $CH_2C_3H_7$], 1.84–1.97 [m, 4H, $CH_{eq}HCHC_4H_9$, $CH_{eq}HCH_2CH_2C(OH)=$, $CH_{eq}CH_2C(OH)=$, $CH(CH_3)_2$], 2.37 [m, 2H, $CH_2C(OH)=$], 2.51 (m, 1H, $CHCH_2CH$), 4.37 (m, 1H, $CHC_4H_9$), 13.28 (s, 1H, OH) | 20.9 [$CH_2CH_2C(OH)=$], 22.1, 23.0, 23.9 [$CH_2CH(CH_3)_2$], 29.1 ($CH_2CHCH_2$), 29.6 [$CH_2C(OH)=$], 33.0 ($CHCH_2CH$), 36.2 ($CH_2CHOCO$), 45.0 ($CH_2C_3H_7$), 78.4 ($CHOCO$), 97.2 ($CCO_2$), 171.9 ($CO_2$), 174.6 $-C(OH)=$] | 225 ($M^{+\cdot}$ + 1, 2), 224 ($M^{+\cdot}$, 16), 206 (10), 141 (31), 123 (100), 122 (17), 95 (11), 67 (12), 57 (10), 55 (28), 43 (20), 41 (36), 39 (16) |

[a] Satisfactory microanalyses obtained for **5a–e**: C ± 0.28, H ± 0.17.
[b] These data coincide with published data.
[c] IR spectrum determined in $CHCl_3$.


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