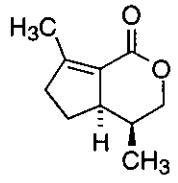
A SHORT ASYMMETRIC SYNTHESIS OF (–)-NEONEPETALACTONE†

Dieter Enders* and Anja Kaiser

Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule,
Professor-Pirlet-Straße 1, 52074 Aachen, Germany
Telefax: (internat.) +49(0)241-8888-127
E-mail: Enders @ RWTH-Aachen.de

Abstract - (4S,4aR)-Neonepetalactone (**6**) was synthesized in high diastereomeric and enantiomeric purity (de, ee ≥ 96 %) in a four step procedure. Key step of the total synthesis is the Michael addition of metalated propanal SAMP-hydrazone ((S)-**1**) to 2-cyclopentenecarboxylate (**2**).

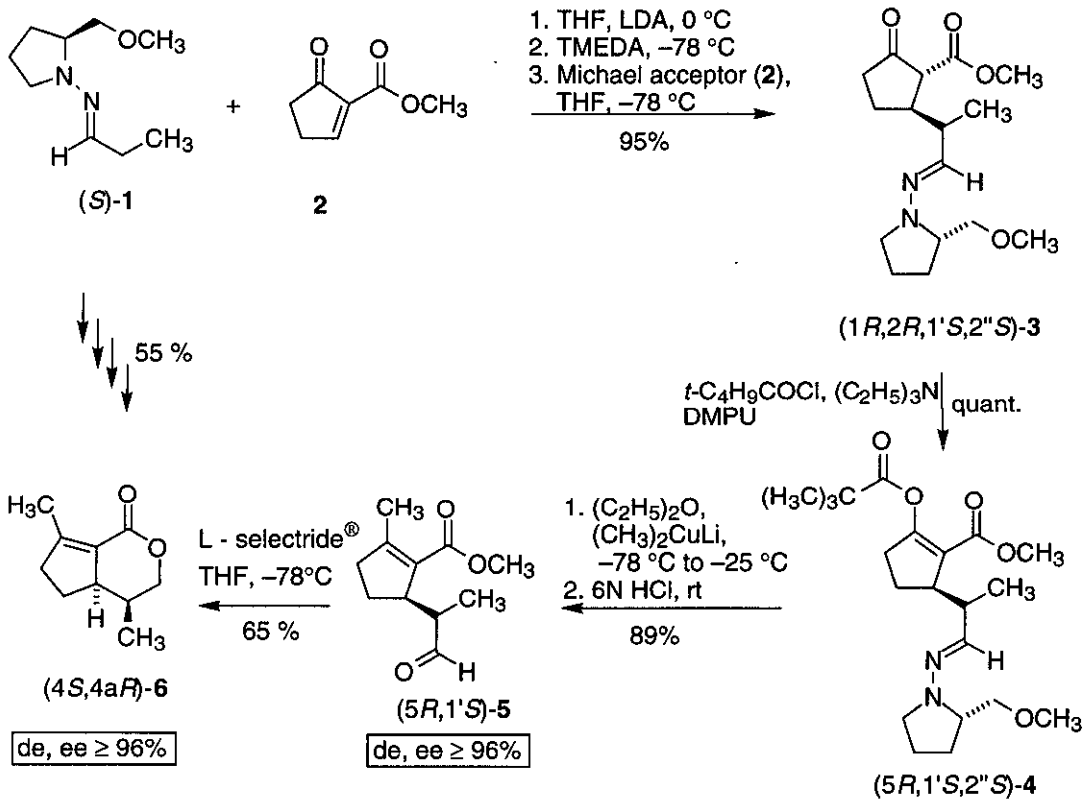
Neonepetalactone has been isolated in 1965 from the leaves and galls of Actinidia polygama by T. Sakan et al., which was found to be quite attractive to cats.[1] The absolute configuration was determined by T. Sakai et al. in 1980.[2] Racemic neonepetalactone has been synthesized via alkylation of a bicyclic β-keto ester with trimethylaluminium.[3] Three „ex chiral pool"-syntheses, starting from (S)-limonene[2,4] and (R)-carvone,[5] and one enantioselective synthesis[6] have been reported so far. We now wish to describe an alternative very short asymmetric synthesis of neonepetalactone employing our SAMP-hydrazone method.[7]



(4S,4aR)-neonepetalactone

As depicted in the Scheme, the propanal-SAMP-hydrazone ((S)-**1**), readily available from propanal and (S)-1-amino-2-methoxymethylpyrrolidine (SAMP), was 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 2-cyclopentenecarboxylate (**2**)[8] resulted in a clean 1,4 addition and the hydrazone Michael adduct (1R,2R,1'S,2''S)-2-[2-(2''-Methoxymethylpyrrolidin-1-

ylimino)-1'-methylethyl]-5-oxo-cyclopentanecarboxylic acid methylester ((1R,2R,1'S,2''S)-**3**) could be obtained in 95% yield by flash chromatography (silica gel, petroleum ether/ ether = 1/ 1).



Scheme

Introduction of the methyl group was achieved by a two step procedure. The hydrazone Michael adduct ((1R,2R,1'S,2''S)-**3**) was converted in quantitative yield and excellent diastereomeric excess (de ≥ 96 %) into the enol pivaloate (5R,1'S,2''S)-2-Pivaloyloxy-5-[2-(2''-methoxymethylpyrrolidin-1-ylimino)-1'methylethyl]cyclopent-1-enecarboxylic acid methylester ((5R,1'S,2''S)-**4**) by treatment with 1.4 equivalents pivaloyl chloride and triethylamine in 1,3-dimethyltetrahydropyrimidin-2-one (DMPU). The de of ((1R,2R,1'S,2''S)-**3**) was determined after conversion into the enol pivaloate ((5R,1'S,2''S)-**4**). The ^{13}C NMR spectrum of ((5R,1'S,2''S)-**4**) showed the existence of a single diastereomer among four possible diastereomeric isomers. The resulting enol pivaloate ((5R,1'S,2''S)-**4**) was purified by flash chromatography (silica gel, petroleum ether/ ether = 1/ 1) and was then treated with 2.5 equivalents of lithium dimethylcuprate. The reaction mixture was quenched and the chiral auxiliary removed by addition of 6N HCl at –25 °C. The 5-substituted 2-methylcyclopentenecarboxylate ((5R,1'S)-**5**) was obtained in 89 %

yield after purification by flash column chromatography (silica gel, petroleum ether/ ether = 1/1) and with excellent diastereomeric and enantiomeric excesses (de, ee ≥ 96 %), that means no epimerization occured under the reaction conditions employed. The ee-determination could be realized by derivatisation with (R,R)-2,3-bis(trimethylsilyloxy)butane under Noyori-acetalisation conditions.[9] The ee-value was determined by ^{13}C NMR spectroscopy via the de of the acetal. In the final step of our total synthesis of (4S,4aR)-neonepetalactone ((4S,4aR)-**6**) the 5-substituted 2-methylcyclopentenecarboxylate ((5R,1'S)-**5**) was reduced with 2 equivalents of L-selectride® in tetrahydrofuran at –78 °C. Neonepetalactone ((4S,4aR)-**6**) was obtained in 65 % yield after purification by flash chromatography (silica gel, petroleum ether/ ether = 1/ 1) and without epimerization under the reaction conditions employed (de, ee ≥ 95 %). The de value was determined by ^{13}C NMR spectroscopy. The ee-value could be determined by ^{1}H NMR shift experiment with the chiral cosolvent (R)-(–)-9-anthryl-2,2,2-trifluoroethanol. The racemic 5-substituted 2-methylcyclopentenecarboxylate (**5**) and the racemic neonepetalactone (**6**) required for comparison were prepared via the corresponding dimethylhydrazone homocuprates according to the method previously described.[10] The assignment of the relative and absolute configurations presented in the Scheme is not only based on the polarimetric data of ((4S,4aR)-**6**), 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-hydrazones.

In conclusion, a very short and highly diastereo- and enantioselective synthesis of (–)-neonepetalactone employing the SAMP-hydrazone method has been developed.

EXPERIMENTAL

All moisture sensitive reactions were carried out using standard Schlenk techniques under argon atmosphere. Solvents were dried and purified by conventional methods prior to use. Tetrahydrofuran was freshly distilled from potassium under argon. Light petroleum refers to the fraction with bp 40 - 80 °C. Reagents of commercial quality were used from freshly opened containers or purified by common methods. Methyllithium (1.6 M (5 %) in ether) and *n*-butyllithium (1.6 M (15 %) in hexane) were purchased from Merck, Darmstadt. L-selectride® was purchased from Aldrich. SAMP[13] and the Michael acceptor (**2**)[14] were synthesized according to literature procedures. - All new compounds gave satisfactory spectroscopic data and elementary analyses.[12k] - Analytical TLC: Merck glass-backed silica gel 60 F_{254} plates. - Column chromatography: Merck silica gel 60, 0.040 - 0.063 mm (230 - 400 mesh) (flash). - Analytical GC: Siemens Sichromat 2 or 3 equipped with a SE-54-CB or OV-1-CB-column (25 m x 0.25 mm), carrier gas nitrogen, FID. - Optical rotations: Perkin-Elmer P 241 polarimeter; solvents of Merck Uvasol quality. - IR-spectra: Perkin-Elmer 1420 and Perkin-Elmer FT/IR 1750. - ^{1}H NMR-spectra (300 MHz), ^{13}C NMR-

spectra (75 MHz): Varian VXR 300 or Gemini 300 (TMS as internal standard). - Mass spectra: Varian MAT212 or Finnigan SSQ 7000 (EI 70 eV). - Elemental analyses: Heraeus CHN-O-Rapid. - HRMS: Finnigan MAT, MAT 95. - Chemical nomenclature was verified by the programme Autonom (version 1.1, Beilstein Informationssysteme GmbH, 1994).

(4S,4aR)-4,7-Dimethyl-4,4a,5,6-tetrahydro-3-H-cyclopenta[c]pyran-1-one, Neonepetalactone (4S,4aR)-6

0.84 mL (0.84 mmol) of L-selectride® was added dropwise to a solution of 82 mg (0.42 mmol) of the purified 5-substituted 2-methylcyclopentenecarboxylate ((5R,1'S)-**5**) in tetrahydrofuran under argon atmosphere at –78 °C. Stirring was continued for 1 h. Then the reaction mixture was quenched with 2 mL water at –78 °C and stirring was continued until the reaction mixture reached room temperature. After addition of ether (20 mL), the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, concentrated in vacuo and the residue was purified by flash column chromatography (silica gel, petroleum ether/ ether = 1/ 1) yielding (4S,4aR)-**6** (45 mg, 65 %) as a colourless solid. - R_f = 0.48 (petroleum ether/ ether = 1/ 1). - mp = 21 °C {lit.,[4]: mp = 21 - 23 °C}. - $[\alpha]_D^{22}$ = –166.7° (c = 0.27, $CHCl_3$) {lit.,[2], natural: $[\alpha]_D^{23}$ = –166.8° (c = 0.31, $CHCl_3$), lit.,[5]: $[\alpha]_D$ = –166.6° (c = 0.02, $CHCl_3$)}. - IR ($CHCl_3$): $\tilde{\nu}$ = 2964 cm^{-1} (s), 2903 (m), 2836 (w), 1711 (s), 1643 (s), 1473 (m), 1454 (m), 1432 (m), 1398 (m), 1378 (s), 1357 (w), 1340 (w), 1270 (m), 1254 (s), 1202 (s), 1165 (s), 1118 (s), 1100 (m), 1074 (w), 1053 (w), 1029 (m), 1010 (s), 994 (m). - ^1H NMR ($CDCl_3$): δ = 0.95 (d, J = 7 Hz, 3 H, $CHCH_3$), 1.55 - 1.70 (m, 1 H, CHHCH), 1.90 - 2.02 (m, 1 H, CHHCH), 2.08 (m, 1 H, $CHCH_3$), 2.22 (m, 3 H, CH_3), 2.26 - 2.60 (m, 2 H, CH_2CCH_3), 3.19 (m, 1 H, CH_2CH), 4.18 (dd, J = 2.35/ 11 Hz, 1 H, CHHO), 4.35 (dd, J = 3.0/ 11.1 Hz, 1 H, CHHO). - ^{13}C NMR ($CDCl_3$): δ = 11.0 ($CHCH_3$), 16.6 (CH_3), 26.2 (CH_2CH), 30.3 ($CHCH_3$), 38.7 (CH_2CCH_3), 47.3 (CH_2CH), 75.5 (CH_2O), 123.0 (CCO_2), 160.8 (CCH_3), 164.3 (CO_2). - MS (70 eV); m/z (%): 167 ($M^{+\cdot}$+1, 3.1), 166 ($M^{+\cdot}$, 45.7), 151 (10), 148 (13), 136 (3), 133 (4), 124 (52), 121 (22), 120 (5), 109 (3), 108 (12), 107 (20), 105 (13), 96 (7), 93 (43), 91 (33), 81 (13), 80 (36), 79 (100), 78 (12), 77 (44), 69 (2), 67 (7), 65 (16), 55 (7), 53 (18), 52 (9), 51 (20), 50 (7). - $C_{10}H_{14}O_2$ (166.2): calcd. 166.0994; found 166.1000 (HRMS).

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