

A SHORT ASYMMETRIC SYNTHESIS OF (-)-NEONEPETALACTONE[†]

Dieter Enders* and Anja Kaiser

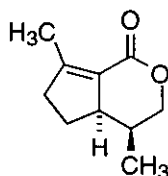
Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule,
 Professor-Pirlet-Straße 1, 52074 Aachen, Germany

Telefax: (internat.) +49(0)241-8888-127

E-mail: Enders @ RWTH-Aachen.de

Abstract - (4*S*,4*aR*)-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 synthesis⁶ have been reported so far. We now wish to describe an alternative very short asymmetric synthesis of neonepetalactone employing our SAMP-hydrazone method.⁷

(4*S*,4*aR*)-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 (1*R*,2*R*,1'*S*,2''*S*)-2-[2-(2''-Methoxymethylpyrrolidin-1-

yield after purification by flash column chromatography (silica gel, petroleum ether/ ether = 1/1) and with excellent diastereomeric and enantiomeric excesses (de, ee $\geq$ 96 %), that means no epimerization occurred 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 ¹³C 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 $\geq$ 95 %). The de value was determined by ¹³C NMR spectroscopy. The ee-value could be determined by ¹H NMR shift experiment with the chiral cosolvent (R)-(-)-9-anthryl-2,2,2-trifluoroethanol. The racemic 5-substituted 2-methylcyclopentenecarboxylate (**5**) and the racemic nonepetalactone (**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-hydrazones¹² 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. Methylolithium (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. SAMP¹³ 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 F₂₅₄ 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. - ¹H NMR-spectra (300 MHz), ¹³C 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 MgSO₄, 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, CHCl₃) {lit.,², natural: $[\alpha]_D^{23}$ = -166.8° (c = 0.31, CHCl₃), lit.,⁵: $[\alpha]_D$ = -166.6° (c = 0.02, CHCl₃)}. - IR (CHCl₃): $\tilde{\nu}$ = 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 (CDCl₃): δ = 0.95 (d, J = 7 Hz, 3 H, CHCH₃), 1.55 - 1.70 (m, 1 H, CHHCH), 1.90 - 2.02 (m, 1 H, CHHCH), 2.08 (m, 1 H, CHCH₃), 2.22 (m, 3 H, CH₃), 2.26 - 2.60 (m, 2 H, CH₂CCH₃), 3.19 (m, 1 H, CH₂CH), 4.18 (dd, J = 2.35/ 11 Hz, 1 H, CHHO), 4.35 (dd, J = 3.0/ 11.1 Hz, 1 H, CHHO). - ¹³C NMR (CDCl₃): δ = 11.0 (CHCH₃), 16.6 (CH₃), 26.2 (CH₂CH), 30.3 (CHCH₃), 38.7 (CH₂CCH₃), 47.3 (CH₂CH), 75.5 (CH₂O), 123.0 (CCO₂), 160.8 (CCH₃), 164.3 (CO₂). - MS (70 eV); m/z (%): 167 (M⁺+1, 3.1), 166 (M⁺, 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). - C₁₀H₁₄O₂ (166.2): calcd. 166.0994; found 166.1000 (HRMS).

ACKNOWLEDGMENTS

This work was supported by the Deutsche Forschungsgemeinschaft (Sonderforschungsbereich 380 and Leibniz prize). We thank Degussa AG, BASF AG, Bayer AG and Hoechst AG for their donation of chemicals.

REFERENCES

† This communication is dedicated to the memory of the late Professor Shun-ichi Yamada.

1. T. Sakan, S. Isoe, S. B. Hyeon, R. Katsumura, T. Maeda, J. Wolinsky, D. Dickerson, M. Slabaugh, and D. Nelson, Tetrahedron Lett., 1965, **46**, 4097.
2. T. Sakai, K. Nakajima, K. Yoshihara, T. Sakan, and S. Isoe, Tetrahedron, 1980, **36**, 3115.
3. T. Hiayama, Y. Morizawa, H. Yamamoto, and H. Nozaki, Bull. Chem. Soc. Jpn., 1981, **54**, 2151.
4. a) J. Wolinsky, T. Gibson, D. Chan, and H. Wolf, Tetrahedron, 1965, **21**, 1247. b) J. Wolinsky and D. Nelson, Tetrahedron, 1969, **25**, 3767.
5. T. Honda, H. Ishige, M. Tsubuki, K. Naito, and Y. Suzuki, Chem. Pharm. Bull., 1991, **39**, 1641.
6. L. R. Pan and T. Tokoroyama, Chem. Lett., 1990, 1999.
7. a) D. Enders in Asymmetric Synthesis, Vol.3; ed. by J. D. Morrison, Academic Press, Orlando, 1984, p. 275. b) D. Enders, Chem. Scripta 1985, **25**, 139. c) D. Enders and M. Klatt in Encyclopedia of Reagents for Organic Synthesis, ed. by L.A. Paquette, Wiley, New York, 1995, p. 3368.
8. Recent examples for asymmetric Michael reactions with cyclopentenone derivatives as Michael acceptor: a) S. Kobayashi, S. Suda, M. Yamada, and T. Mukaiyama, Chem. Lett., 1994, 97. b) H. Sasai, T. Arai, and M. Shibasaki, J. Am. Chem. Soc., 1994, **116**, 1571. c) A. Kawara and T. Taguchi, Tetrahedron Lett., 1994, **35**, 8805. d) A. Bernardi, K. Karamfilova, G. Boschini, and C. Scolastico, Tetrahedron Lett., 1995, **36**, 1363. e) S. E. Denmark and J. H. Kim, J. Org. Chem., 1995, **60**, 7535. f) K. Tanaka, Y. Ohta, and K. Fuji, J. Org. Chem., 1995, **60**, 8036.
9. a) D. Parker, Chem. Rev., 1991, **91**, 1441. b) H. Hiemstra and H. Wynberg, Tetrahedron Lett., 1977, 2183. c) T. Tsunoda, M. Suzuki, and R. Noyori, Tetrahedron Lett., 1980, **21**, 1357.
10. E. J. Corey and D. Enders, Chem. Ber., 1978, **111**, 1362.
11. a) D. Enders, H. J. Scherer, and J. Runsink, Chem. Ber., 1993, **126**, 1929. b) D. Enders, H. J. Scherer, and G. Raabe, Angew. Chem., 1991, **103**, 1676; Angew. Chem., Int. Ed. Engl., 1991, **30**, 1664.
12. a) D. Enders and K. Papadopoulos, Tetrahedron Lett., 1983, **24**, 4967. b) D. Enders, K. Papadopoulos, B. E. M. Rendenbach, R. Appel, and F. Knoch, Tetrahedron Lett., 1986, **27**, 3491. c) D. Enders and B. E. M. Rendenbach, Tetrahedron, 1986, **42**, 2235. d) D. Enders and B. E. M. Rendenbach, Chem. Ber., 1987, **120**, 1223. e) D. Enders, A. S. Demir, and B. E. M. Rendenbach, Chem. Ber., 1987, **120**, 1731. f) D. Enders, A. S. Demir, H. Puff, and S. Franken, Tetrahedron Lett., 1987, **28**, 3795. g) D. Enders, S. Müller, and A. S. Demir, Tetrahedron Lett., 1988, **29**, 6437. h) D. Enders, K. Papadopoulos, and E. Herdtweck, Tetrahedron, 1993, **49**, 1821. i) D. Enders, H. Wahl, and K. Papadopoulos, Liebigs Ann. Chem., 1995, 1177. j) D. Enders and A. Kaiser, Synthesis, 1996, 209. k) D. Enders and A. Kaiser, Liebigs Ann., submitted.
13. a) D. Enders and H. Eichenauer, Chem. Ber., 1979, **112**, 2933. b) D. Enders, P. Fey, and H. Kipphardt, Org. Synth. Proced. Int., 1985, **17**, 1. c) D. Enders, P. Fey, and H. Kipphardt, Org. Synth., 1987, **65**, 173.
14. J. M. Renga and H. J. Reich, Org. Synth., 1979, **59**, 58.

Received, 20th November, 1996