Tetrahedron Letters,Vol.28,No.2,pp 183-186,1987
Printed in Great Britain

0040-4039/87 $3.00 + .00
Pergamon Journals Ltd.

EPC-SYNTHESES VIA ASYMMETRIC DIELS-ALDER REACTIONS/RETRO DIELS-ALDER REACTIONS I: (R)- AND (S)-MATSUTAKE ALCOHOL, (R)- AND (S)-SARCOMYCIN METHYL ESTER[1]

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Summary: Enantiomerically pure Diels-Alder adducts, obtained by asymmetric Diels-Alder reaction, were modified diastereoselectively and the products cleaved by retro Diels-Alder reaction to give chiral compounds [(R)- and (S)-1-octen-3-ol, (R)- and (S)-sarcomycin methyl ester] of high enantiomeric purity.

The retro Diels-Alder reaction of modified Diels-Alder adducts has found numerous applications in the synthesis of sensitive olefins, among them a variety of important natural products[2]. We felt that the scope of this methodology might considerably be expanded by exploiting the fact that Diels-Alder adducts are often chiral: enantiomerically pure compounds are expected to result when enantiomerically pure chiral Diels-Alder adducts are modified diastereoselectively and products, possibly after purification from diastereomeric contaminants, are subjected to the retro Diels-Alder reaction by flash vacuum pyrolysis (FVP).

Experimental implementation of this concept critically depends on the availability of enantiomerically pure Diels-Alder adducts. Recent development by this group of kg-scale asymmetric Diels-Alder reactions[3] has solved this problem for a wide variety of structures. Accordingly, we have initiated a programme to pursue the concept stated above in a systematic way. As first synthetic targets we chose the compounds of obvious biological relevance stated in the title.

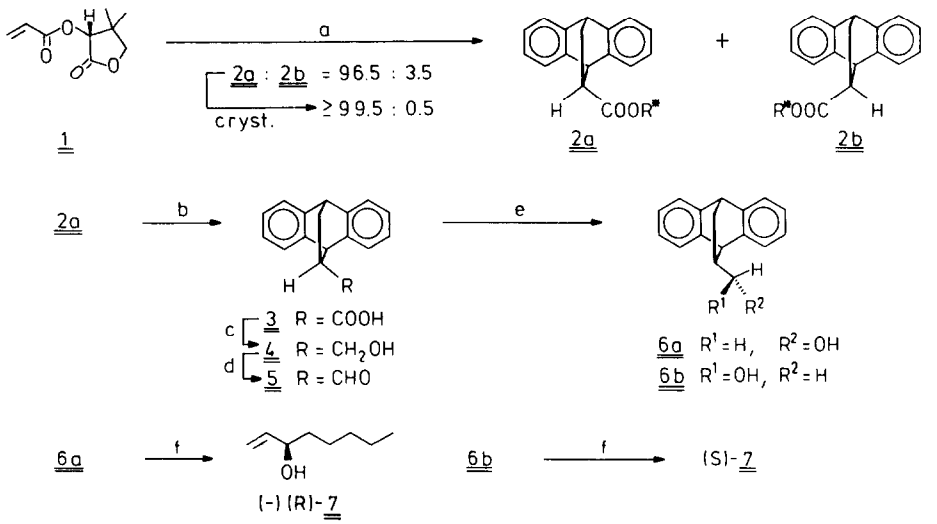
(-)(R)-1-Octen-3-ol (**7**, Matsutake alcohol) is an important flavour compound of mushrooms[4]. Apart from interest in this aspect we chose this compound as a target in order to test whether a retro Diels-Alder process furnishing sensitive allylic alcohol derivatives would be accompanied by racemization. As chiral template (cf. Scheme 1) (11S)-9,10-dihydro-9,10-ethanoanthracene-11-carboxylic acid (**3**) was used. This compound is easily available on a large scale by Lewis acid catalyzed asymmetric Diels-Alder reaction. Thus, the reaction (Scheme 1) of anthracene with the acrylate of (R)-pantolactone (**1**)[3b], a commercially available reagent, furnished the diastereomeric adducts **2a** and **2b** with a diastereoselectivity of 96.5:3.5 (HPLC[5] analysis). From the crude product pure **2a** (mp 213-214 °C)[6] was obtained in 82 % yield[5] by twice crystallizing from ethanol. Saponification of **2a** gave the carboxylic acid (S)-**3** in 97 % yield {$[\alpha]_D^{20}$ 7.2 c = 2, $CHCl_3$}. Reduction of (S)-**3** with LAH gave the alcohol (S)-**4** (99 %) which was transformed by Swern oxidation into the aldehyde (S)-**5** (87 %, mp 123-125.5 °C). Enantiomeric purity of 98 ± 0.5 % was established for this compound by reduction with LAH to give (S)-**4** followed by formation of diastereomeric carbamates with (R)- and (S)-1-(1-naphthyl)-ethyl isocyanate and HPLC analysis.

The aldehyde (S)-**5** was reacted with pentyl organometallic compounds to give the diastereomers **6a** and **6b** which could be separated on a multigram scale by MPLC. The best results were obtained by reacting n-pentyl magnesium bromide with the $TiCl_4$ complex of (S)-**5** (87 % yield, **6a** : **6b** = 2.6:1). After MPLC separation, the isomers were individually O-silylated to increase volatility and the silyl ethers were subjected to FVP (quartz tube, 660 °C/0.005 mmHg). Products collected in a dry ice trap were hydrolyzed to give (R)- and (S)-**7**, after flash chromatography, in overall yield (from **6**) of 95 and 89 %, respectively. The enantiomers displayed optical rotations identical in absolute values (R)-**7**: $[\alpha]_D^{20}$ -18.4 (neat, not normalized with respect to density). Enantiomeric purities were determined to be 98.0 0.5 %, within the range of precision identical to that of the aldehyde (S)-**5**. Consequently, the retro Diels-Alder process proceeds without notable racemization. Current work is directed at improving the diastereoselectivity of the addition step by placing a Lewis basic substituent at the bridgehead positions of the dibenzobicyclo.2.2.2.octane derivatives **2-5**.

The antibiotic sarcomycin, an antitumor agent, and its methyl ester (**14**, Scheme 2) have been targets of numerous synthetic efforts, commonly directed at the racemic compounds[7]. Two syntheses have been reported for (-)(R)-sarcomycin[8]; however, the first[9] has apparently furnished a mixture of regioisomers[8]; the second[10] was carried out with racemic material with the exception of the first three of 8 steps. This is accordingly a formal synthesis; but there is no doubt that it would succeed if it were fully carried through.

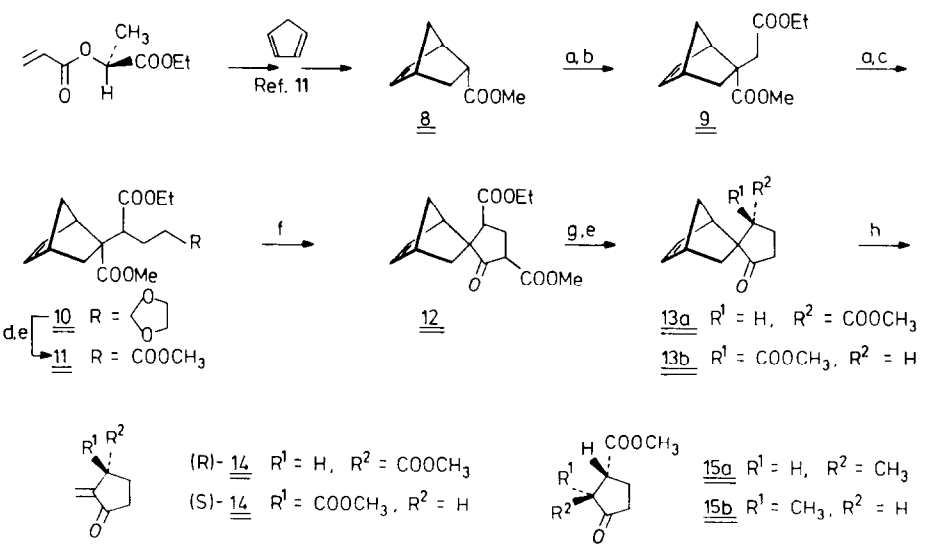
In our synthesis (Scheme 2), methyl (1R,2R)-5-norbornene-2-carboxylate (**8**) was used as chiral template. Enantiomerically pure **8** is easily available on large scale from the reaction of the acrylate of (S)-ethyl lactate with cyclopentadiene[11]. Alkylation of **8** with ethyl bromoacetate proceeded diastereoselectively to give the exo substituted[12] diester **9** in 77 % yield. Preparation of **12** from **9** was carried out in stepwise manner as attempted one-pot Michael addition/Dieckmann cyclization[7b] gave unsatisfactory results. Thus, alkylation of **9** with the ethylene acetal of 3-iodopropanal gave **10** (72 %); subsequent acetal cleavage, oxidation and esterification then furnished the diester **11** (91 %) and, finally, Dieckmann condensation (88 %) the desired spirocyclic **12**[13]. Saponification/decarboxylation followed by esterification yielded a 1.2:1 mixture of the diastereomers **13a** and **13b** (62 %) which could easily be separated by MPLC (**13a**: oil, **13b**: mp 87.5-88 °C). As in the case of **6a,b**, the retro Diels-Alder step gave excellent results: **13a** and **13b** furnished (-)(R)- and (+)(S)-**14** in 92 and 93 % yield, respectively. Both compounds were pure according to ^{1}H-NMR and elemental analysis[14]. However, as had previously been pointed out[7a], **14** has to be kept in dilute cooled solutions (CH_2Cl_2, benzene) in order to avoid polymerization which is rather rapid in the condensed state. It was not possible for that reason to determine the optical rotation of **14** accurately. Furthermore, various attempts to determine enantiomeric purity[15] were not successful. For unambiguous characterization, (R)-**14** was hydrogenated to yield a mixture of cis-trans isomers **15a,b** with **15b** in excess (HPLC analysis[16] **15a**:**15b** = 1:2.3). Equilibration (NEt_3, **15a**:**15b** = 2.6:1) followed by MPLC separation gave pure **15a** with optical rotation of $[\alpha]_D^{20}$ +70 (c = 0.55, methanol), the same value (within the range of precision of measurement) as has been reported for samples obtained from natural sarcomycin[17]. This indicates for another sensitive compound that the retro Diels-Alder step is devoid of racemization[18]

Scheme 1



R*OH = (R)-Pantolactone; (**a**) Anthracene, 0.75 equiv. of $TiCl_4$, CH_2Cl_2, +25 °C; (**b**) LiOH, THF-H_2O 5:4, rt; (**c**) LAH, THF, rt; (**d**) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; -78 °C → rt; (**e**) n-$C_5H_{11}MgBr$/CH_2Cl_2 added to **5**/$TiCl_4$, CH_2Cl_2, -78 °C; (**f**) 1. $CH_3CON(CH_3)Si(CH_3)_3$, CH_2Cl_2, 2. FVP: 660 °C/0.005 Torr, 3. AcOH, CH_3OH/H_2O.

Scheme 2



(**a**) 1.1 Equiv. of LDA, THF, -75 °C; (**b**) $BrCH_2COOEt$, DMPU, THF; (**c**) 2-(2-Iodoethyl)-1,3-dioxolane DMPU, THF; (**d**) 1. $CH_3COOH-H_2O$ 1:1, reflux, 2. Ag_2O, KOH, EtOH, rt; (**e**) CH_2N_2, Et_2O, -10 °C; (**f**) KO-t-Bu, THF, -70 °C; (**g**) 0.4 N NaOH in MeOH-H_2O 1:1, 100 °C; (**h**) FVP: 650 °C/0.02 Torr.

Acknowledgements: This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

1. The work on the synthesis of (R)- and (S)-Matsutake alcohol, first illustrating the concept presented in this paper, was presented (G. H.) at the International Seminar on Modern Synthetic Methods 1986, Interlaken, April 18th 1986, and in various lectures at universities in Switzerland and the FRG.

2. Reviews: (a) M.Karpf, Angew.Chem. **98**, 413 (1986); Angew.Chem.Int.Ed.Engl. **25**, 414 (1986); (b) M.-C.Lasne, J.-L.Ripoll, Synthesis **1985**, 121; references cited therein.

3. (a) Review: G.Helmchen, R.Karge, J.Weetman, in R.Scheffold (Ed.), Modern Synthetic Methods 1986, vol. 4, p. 262-306, Springer, Heidelberg; (b) T.Poll, A.Sobczak, H.Hartmann, G.Helmchen, Tetrahedron Lett. **1985**, 3095.

4. (a) W.Freitag, K.H.Ney, J.Chromatogr. **41**, 473 (1969); (b) A.Mosandl, G.Heusinger, M.Gessner, J.Agric. Food Chem. **34**, 119 (1986); (c) W.F.Wood, M.Fessler, J.Chem.Ed. **63**, 92 (1986).

5. If it is not stated otherwise, LC separations were carried out with petroleum ether/ethyl acetate mixtures of suitable eluotropicity.

6. All new compounds described herein gave correct elemental analyses and spectra.

7. (a) J.N.Marx, G.Minaskanian, J.Org.Chem. **47**, 3306 (1982); (b) M.Kodpinid, T.Siwapinyoyos, Y.Thebtaranonth, J.Am.Chem.Soc. **106**, 4862 (1984); (c) A.Misumi, K.Furata, H.Yamamoto, Tetrahedron Lett. **1984**, 671; (d) P.G.Baraldi, A.Barco, S.Benetti, G.P.Pollini, E.Polo, D.Simoni, J.Chem.Soc. Chem.Commun. **1984**, 1049; (e) R.D.Baker, R.B.Keen, M.D.Morris, R.W.Turner, ibid. **1984**, 987; (f) T.Cohen, Z.Kosarych, K.Suzuki, L.Yu, J.Org.Chem. **50**, 2965 (1985); literature cited.

8. Absolute configuration of sarcomycin and dihydrosarcomycin: R.K.Hill, P.J.Foley Jr., L.A.Gardella, J.Org.Chem. **32**, 2330 (1967).

9. (a) K.Toki, Bull.Chem.Soc.Jpn. **30**, 450 (1957); (b) K.Toki, ibid. **31**, 333 (1958).

10. R.K.Boeckman Jr., P.C. Naegely, S.D.Arthur, J.Org.Chem. **45**, 752 (1980); R.K.Boeckman Jr., J.J.Napier, E.W.Thomas, R.I.Sato, J.Org.Chem. **48**, 4152 (1983).

11. T.Poll, G.Helmchen, B.Bauer, Tetrahedron Lett. **1984**, 2191.

12. We were not able to detect (HPLC, NMR) the endo isomer of **9** in the product; cf. A.P. Krapcho, E.A.Dundulis, J.Org.Chem. **45**, 3236 (1980).

13. Compounds **10-12** were mixtures of (enantiomerically pure) diastereomers which were not individually characterized.

14. The elemental analyses were carried out with polymerized material. ^{1}H-NMR (300 MHz, $CDCl_3$) 2.10-2.40 (m, 3H), 2.50-2.61 (m, 1H), 3.55-3.82 (m, 1H), 3.73 (s, 3H), 5.58 (dd, J = 2.4, J'= 0.6 Hz, 1H), 6.15 (d, J = 2.7 Hz, 1H).

15. Examined by ^{1}H-NMR with shift reagent $Eu(hfc)_3$ and, by courtesy of Prof. Schurig (Tübingen), complexation gas chromatography.

16. Isomer ratios correspond to HPLC relative peak areas (refractive index detector).

17. (a) I.R.Hooper, L.C.Cheney, M.J.Cron, O.B.Fardig, D.A.Johnson, D.L.Johnson, F.M.Palermiti, H.Schmitz, W.B.Wheatley, Antibiot.Chemotherapy **5**, 585 (1955); (b) S.Tatsuoka, A.Miyake, M.Inoue, S.Wada, H.Iwasaki, K.Ogata, J.Antibiotics **9B**, 157 (1960); Chem.Abstr. **54**, 9784 (1960).

18. For definitive corroberation of this statement a procedure for the determination of the enantiomeric purity of dihydrosarcomycin (**16a**) is being worked out in this laboratory.

(Received in Germany 10 October 1986)