to have a first estimate of the magnitude τ_c. Using the values in *Table 1* and P–C–H, P–C–C–H (staggered, aliphatic chains) and P–C–C–H (aromatic) distances of 2.41, 3.54 and 3.89 Å respectively, we calculate τ_c values between 10^{-10} and 10^{-11} sec for our complexed P-atoms.

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87. Syntheses of (+)-(*S, S*)-(*cis*-6-Methyltetrahydropyran-2-yl)acetic Acid and of (−)-(*R, R*)-Didesoxy-pyrenophorine Using a New d^5-Reagent[1][2]

Preliminary communication

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(1.III.79)

Summary

The Li/K-derivative **6** is used to synthesize the title compounds (**3a** and **4a**) in enantiomerically pure form from (−)-(*S*)-propylene epoxide. The C,C bond

[1] The work described here was done in 1977, see PhD-Thesis of *M. P.*, Justus-Liebig-Universität, Giessen, Oct. 1978.

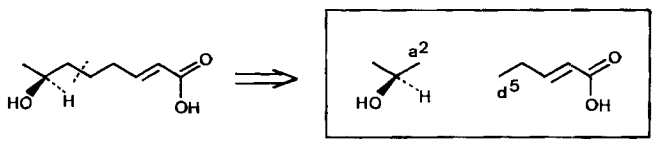
[2] The acceptor (a)/donor (d) nomenclature of synthetic methodology and a classification of the methods of reactivity *umpolung* are described in a review article [3]. According to this nomenclature, an enolate, an enone, and a dienone are d^2-, a^3-, and a^5-reagents, respectively.

forming key step leading to the hydroxyketone **7** is followed by cyclization (→**8**), *Beckmann* cleavage (→**9b**) and hydrolysis to **3a** (recently isolated from civet). Base treatment of **3a** opens the ring (**10**) to give the hydroxyacid **1** which is cyclized to the macrolide **4a**. The synthetic usefulness of the highly nucleophilic doubly reduced dienone system **6** as d^5-reagent (see synthons **2**) is thus demonstrated.

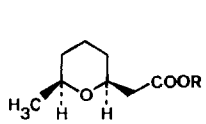
The unsaturated hydroxyacid **1** should be a common precursor to the heterocycles **3a** and **4a**. The THP-derivative **3a** was just isolated from civet *(viverra civetta)* [1]; its structure and *cis*-configuration was proved by IR., ^{1}H-NMR. and mass spectroscopy as well as by synthesis of the *d,l*-form (hydrogenation of the *Diels-Alder* product from methyl vinyl ketone and ethyl vinyl ether, hydrolysis and *Horner* olefinition); the amount of material obtained from the natural source was too small for optical activity to be measured [1].

The macrolide **4a** is interesting for two reasons: (i) it is a potential intermediate for the synthesis of pyrenophorine **4b**, and (ii) our previous results with *d-*, *l-*, *d,l-*, meso- and desmethyl-pyrenophorine, showing that chirality and substitution of the heterocyclic skeleton of **4b** have little effect on its antimicrobial activity, suggested a test of **4a** lacking two carbonyl functions [2].

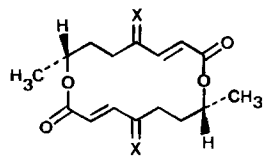
The enantiomer syntheses of **3a** and **4a** use the a^2/d^5-combination[2]) shown in the synthon box **2**. The chiral pool [2] [4] [5] compound (−)-(*S*)-methyloxirane **5** (from lactic acid [4]) serves as a^2-reagent, the Li/K derivative **6** of a dienone dianion



1 **2**



3a R = H
3b R = CH_3



4a X = H_2
4b X = O

(*LUMO-filled π-system*, redox umpolung of reactivity)[2]) as the d^5-component[3]). The compound **6** is generated from the γ,δ-unsaturated ketone[4]) by sequential treatment with KH (1 h, RT.) and *sec*-butyllithium/TMEDA 1:2 in THF (4.5 h, −78 to 0°),

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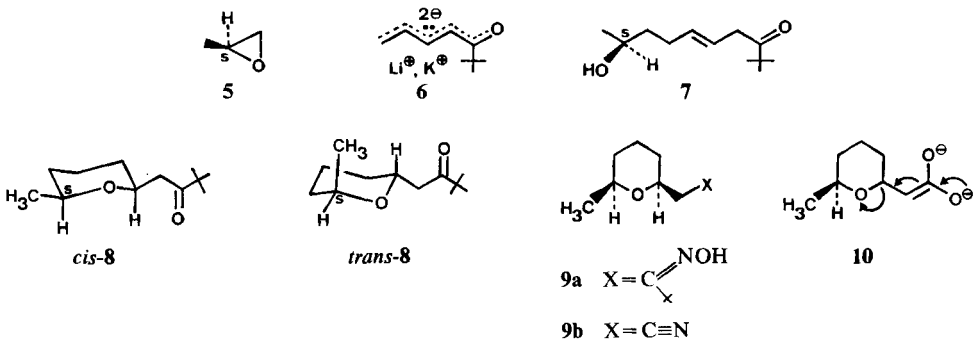
[3]) Other d^5-reagents have protected carbonyl groups [6], are based on acetylene chemistry [7], or involve thio-*Claisen* rearrangements [8].

[4]) 2,2-Dimethyl-6-hepten-3-one, from pinacolone and allyl bromide using the enhydrazinate method [9]. $[H_2C{=}C(t\text{-}C_4H_9)[\overset{\ominus}{N}{-}N(CH_3)_2]$, *cf.* enolate $[C{=}C(R)O^{\ominus}]$ and enaminate $[C{=}C(R)(\overset{\ominus}{N}R')]$.



like the previously reported phenyl substituted analogue [10][5]). Reaction of the alkali derivative **6** with the epoxide **5** (−78 to +25°, 14 h; CH_3COOH quench at −78°) furnishes the *E*-hydroxyketone **7**[6]) as the sole product in 50% yield. Short term treatment[7]) of **7** with sodium methoxide causes cyclization to a (3:2)-mixture of *cis*- and *trans*-**8**, while after several days the thermodynamically controlled product *cis*-**8** is quantitatively isolated[7]). The oxime **9a**[8]) of this ketone undergoes *Beckmann* type-II cleavage to the nitrile **9b**[9]) which was hydrolyzed[10]) to yield (+)-(*S*, *S*)-**3a** (55% from **7**). The methyl ester **3b** is identical with the compound from civet, the present synthesis establishes the absolute configuration (sense of chirality) of the natural product as soon as enough material becomes available for measurement of optical activity or for a ^{1}H-NMR.-spectrum with chiral shift reagent[11]).

For the macrolide **4a** synthesis, the THP-ring of **8** and **9** can be considered as a protection of the olefinic double bond against side reactions during oxime formation, *Beckmann* rearrangement, and nitrile hydrolysis. The ring can be opened through the dianion of the THP-acetic acid as indicated by the arrows in formula **10** (1.95 equiv. of LDA, THF, −78 to 0°, 4 h; 85% yield) to give the desired (*S*)-hydroxyacid **1**. Treatment of **1** in THF/toluene 1:9 with azodicarboxylate/triphenylphosphine (*Mitsunobu* method) under the conditions used in the pyrenophorine and vermiculine syntheses [2] led to the isolation of 46% of the 'dimer' (−)-(*R*, *R*)-**4a**. All reactions were also carried out with racemic material, in which case a readily separated (SiO_2 chromatography) *meso*/*d*,*l*-mixture **4a** resulted. None of the di-

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5) The removal of the phenyl group from products of **6**, C_6H_5 instead of *t*-C_4H_9 [10], turned out to be too difficult for synthetic applications[1]).

6) The assignment of *Z*-configuration to some of the products of **6**, C_6H_5 instead of *t*-C_4H_9 [10], was erraneous. All products of type **7** from a variety of dianion derivatives **6** and different electrophiles have *E*-configuration[1]).

7) 20 ml THF/CH_3OH (1:1), equivalent amounts of hydroxyketone and $NaOCH_3$ (*ca.* 2 mmol). Kinetic product after 1–2 h at RT., thermodynamic product after 3–4 d.

8) Two equivalents each of NaOAc and $NH_2OH \cdot HCl$ per equivalent of ketone, 80% aq. CH_3OH, 6–10 h reflux.

9) 1 mmol of oxime, 1.1 equivalents of PCl_5 in 20 ml of ether, mixing at 0°, stirring for 18 h at RT., *cf.* [11].

10) 15 ml 50% aq. KOH-solution, 25 ml ethylene glycol, and 10 mmol of nitrile are heated at 150° for *ca.* 10 h, *cf.* [12].

11) B.p., IR. and NMR. spectra were identical with those of authentic material [1].

Table. *Some physical and spectroscopic data of products and intermediates of the syntheses of* **3a** *and* **4a** (b.p. from Kugelrohr distillations)

Precursor to **6**[4]). B.p. 70–72°/30 Torr; $n_D^{21.5} = 1.4293$; ^{1}H-NMR.: 1.10 (*t*-C_4H_9).

7. B.p. 70°/0.006 Torr; $n_D^{21} = 1.4622$; $[\alpha]_D^{21} = +37.89°$ ($c = 2$, benzene); IR.: 1710 (C=O), 1650 (C=C), 940 (*trans*-C=C); ^{1}H-NMR.: 1.13 (*t*-C_4H_9).

cis-**8**. B.p. 56°/1 Torr; $n_D^{21} = 1.4454$; $[\alpha]_D^{21} = +37.79°$ ($c = 2$, benzene); ^{1}H-NMR.: 1.06 (*t*-C_4H_9), 1.03 (*d*, 6, CH_3), 2.23 and 2.70 (2 *d*×*d*, $J = 16.5$ and 6.0, α-CO–CH_2).

9b. B.p. 80°/1 Torr; $n_D^{21} = 1.4493$; $[\alpha]_D^{21} = -1.75°$ ($c = 1.4$, benzene); IR.: 2250 (C≡N); ^{1}H-NMR.: 1.13 (*d*, $J = 7$, CH_3), 2.4 (*m*, α-NC–CH_2).

3a (*d,l*-form). M.p. 50–52° (pentane) (52–53° [1]).

(*S,S*)-**3a**. B.p. 150°/0.004 Torr (viscous liquid); $[\alpha]_D^{22} = +32.86°$ ($c = 1.05$, benzene); ^{1}H-NMR.: 1.1 (*d*, $J = 7$, CH_3), 2.28 and 2.53 (2 *d*×*d*, $J = 16$ and 7, α-$COCH_2$).

3b. B.p. 70°/0.6 Torr; $n_D^{20} = 1.4402$; $[\alpha]_D^{21} = +31.97°$ ($c = 1.2$, benzene); IR.: 1740 (C=O); ^{1}H-NMR.: 1.1 (*d*, $J = 7$, CH_3), 3.6 (OCH_3), 2.23 and 2.46 (2 *d*×*d*, $J = 15$ and 6, α-CO–CH_2), 3.2–3.8 (*m*, 2 α-O–CH).

d,l-**1**. B.p. 200°/0.004 Torr; ^{1}H-NMR.: 1.2 (*d*, $J = 6$, CH_3), 5.83 (*d*, $J = 16$, COCH–C), 7.1 (*d*×*t*, $J = 16$ and 6, CH_2CH=C).

meso-**4a**. M.p. 60.5–61.5°; ^{1}H-NMR.: 1.23 (*d*, $J = 7$, CH_3), 4.9 (*m*, α-O–CH), 5.83 (*d*, $J = 16$, COCH–C), 6.8 (*d*×*t*, $J = 16$ and 6, CH_2CH=C).

d,l-**4a** (slower moving on preparative SiO_2 layer chrom., 30% ether in pentane). M.p. 59–60°; ^{1}H-NMR.: superimposable with that of *meso*-form.

(–)-(*R,R*)-**4a**. M.p. 49–50°; $[\alpha]_D^{21} = -32.45°$ ($c = 0.5$, benzene); ^{13}C-NMR.: 165.9 (C=O), 148.2 and 122.7 (C=C), 70.2 (*d*, CHO), 33.2, 30.7 and 22.0 (*t*, CH_2), 19.1 (*qa*, CH_3).

desoxy-pyrenophorines **4a** thus obtained showed antibiotic activity with the microorganisms tested [2][12]). This proves that the γ-keto-α,β-unsaturated ester moiety (*Michael* acceptor) is essential for the biochemical mechanism.

Some characteristic data of the new compounds are listed in the *Table*, they were all obtained in analytically pure form (±0.3% in elemental analyses). Reagents of type **6** can obviously also be used for the syntheses of other THF-[10] and THP-containing natural products.

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