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DETERMINATION OF ABSOLUTE STRUCTURE OF (-)-OUDEMANSIN B

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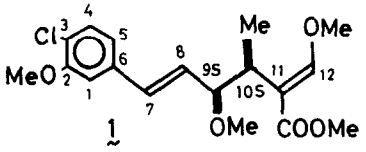
Summary: (-)-Oudemansin B (1) synthesized from (2R,3S)-2,3-epoxybutyrate 2 based on microbial asymmetric reduction of ketone was proved to be identical with natural oudemansin B (1), which established that the absolute configuration of 1 is 9S, 10S.

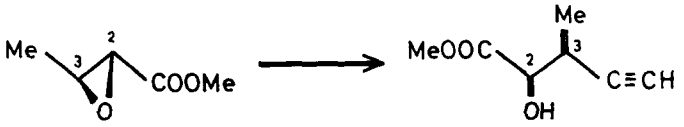
Oudemansin B (1) is an antibiotics isolated from mycelial cultures of Xerula melanotricha and inhibits the growth of a wide variety of saprophytic and phytopathogenic fungi at very low concentration.[1] The structure has been deduced by spectroscopic methods and recently syn-C_9-OMe, C_{10}-Me structure has been confirmed by the synthesis of (±)-1 by Kallmerten et al.[2] However, the absolute configurations of these two chiral centers are remained unknown.

We now report that the absolute structure of 1 was established as 9S, 10S by the total synthesis starting from chiral intermediate of known absolute structure.



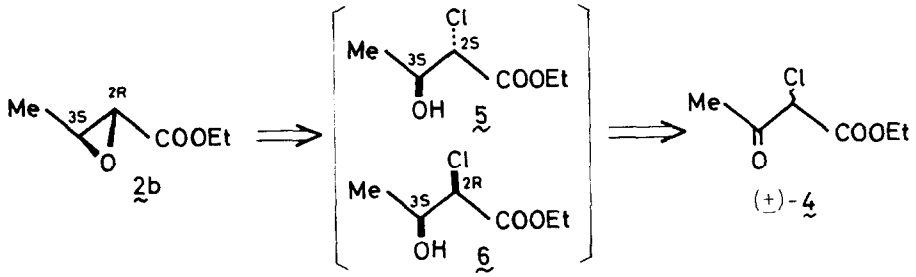
1

It has been reported that silyl acetylide attacks preferentially on C-3-position of (±)-trans-(2,3)-epoxybutyrate 2a producing (±)-syn-C_2-OH, C_3-Me ester 3,[3] from which (±)-1 is expected to be derived by following a similar route already used in oudemansin A synthesis.[2,4] Thus, initially we focussed our attention to the synthesis of optically active 2.

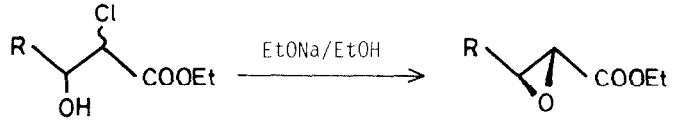


(±)-trans 2a (±)-trans 3

We intended to synthesize (2R,3S)-epoxide 2b by a microbial enantioselective reduction of (±)-2-chloro-3-oxobutyrate 4 followed by base catalyzed epoxidation.

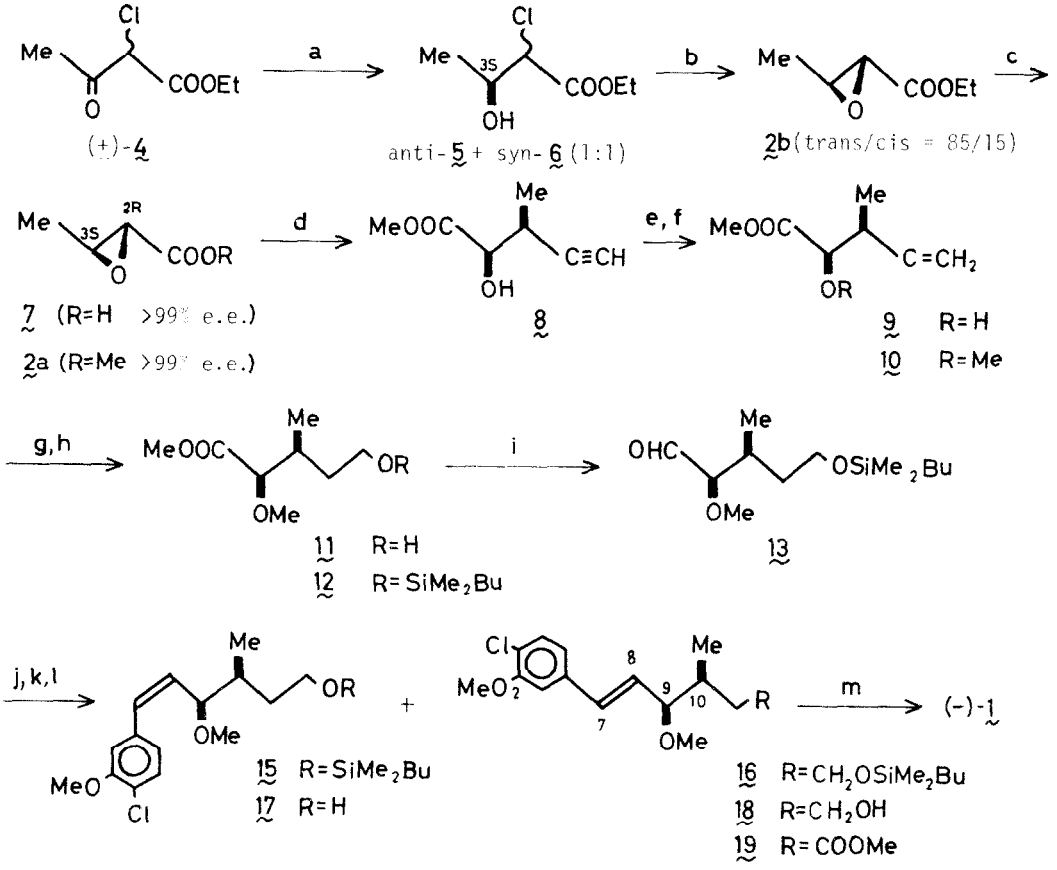


The main drawback of this biological method is that along with a desired optically pure anti-compound 5, the isomeric syn-compound 6 is presumed to be produced in almost equal quantity, because we have encountered with this difficulties in all biological reductions producing two chiral centers.[5] However, in this particular case, formation of the syn-isomer 6 can not be a serious obstacle, since Mukaiyama et al. have already shown that sodium ethoxide promoted epoxidation of a mixture of (±)-syn- and anti-2-chloro-3-hydroxy ester i affords (±)-trans-epoxide ii preferentially (cis/trans = 15/85 ~ 1/99).[6]



(±)-syn, anti-mixture i (±)-trans ii

In fact, reduction of commercially available 4 with baker's yeast (Saccharomyces cerevisiae) afforded a 1:1 mixture of chlorohydrin 5 and 6 in 68% yield. The mixture was treated



a; baker's yeast b; NaOEt/EtOH c; 1) OH^- 2) H^+ 3) brucine 4) OH^- 5) H^+ 6) CH_2N_2
d; 1) $Et_2AlC{\equiv}C\text{-}SiMe_3$ 2) $KF/H_2O/DMSO$ e; H_2/Lindlar f; MeI/Ag_2O/DMF g; 1) disiamylborane/THF, 6hr 2) 30% H_2O_2/3N-NaOH, 30 min h; $^tBuMe_2SiCl$/imidazole/DMF i; DIBAL/toluene j; n-BuLi/THF, 14 k; $Bu_4N^+F^-.3H_2O$ l; 1) Jones oxidation 2) CH_2N_2 m; 1) HCOOMe/LDA/THF, -78-0°C 2) OH^- 3) H^+ 4) CH_2N_2/MeOH

with NaOEt giving a mixture of cis and trans epoxy ester in 84% yield, whose ratio was, from NMR data, found to be 85:15,[7] trans epoxide 2b[8] being predominating as expected. In order to eliminate the contaminated cis-epoxide, the 85:15 mixture was converted, after hydrolysis, into brucine salt. On one recrystallization of the crude salt followed by base treatment, the isomer free, optically pure (>99% e.e.)(2R,3S)-epoxy carboxylic acid 7 was obtained in over all 37% yield from a mixture of 5 and 6, which was treated with CH_2N_2 to give the desired pure 2a.[9,10] By applying Roush's method,[3] 2a was then converted into the acetylene 8[13] in 60% yield. Partial hydrogenation of 8 using Lindlar catalyst afforded olefin 9 in 86% yield. Methylation of 9 with MeI in the presence of Ag_2O produced methoxy ester 10,[9,14] which was hydroborated with disiamylborane in THF to give alcohol 11 (IR (CCl_4) 3625, 3470 cm^{-1}) in 38% yield from 9. After protection of primary OH in 11 with $^tBuMe_2SiCl$ (93%), the resulting silyl ether 12[9,15] was reduced with DIBAL affording aldehyde 13 (IR (CCl_4) 1735 cm^{-1}, NMR ($CDCl_3$) δ : 9.682, d, J=1.8 Hz). 13 was, without purification, allowed to react with phosphonium salt 14[16] in the presence of n-BuLi giving a 1:1 mixture of the condensation products (cis-15 and trans-16) in 70% yield from 12. After desilylation with fluoride ion ($Bu_4N^+F^-.3H_2O$), the mixture was separated by SiO_2 column chromatography. cis-17[9,17] and trans-18[9,17] were obtained in 45.2% and 35.3% yields, respectively. The trans-syn-alcohol 18 was oxidized with CrO_3 and the resulting acid was esterified with CH_2N_2 giving methyl ester 19[9,18] in 75% yield. Formylation of 19 with methyl formate in the presence of LDA in THF at -78° (then to 0°C) followed by CH_2N_2-MeOH treatment afforded (-)-oudemansin B (1) in 31% yield after purification by HPLC. The physical data (CD, $[\alpha]_D$, MS, NMR and UV) of the synthetic (-)-1 were identical with those of natural oudemansin B (1). The absolute configuration of natural oudemansin B (1) was thus established as shown in 1.

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References and Notes

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2) J. Kallmerten and M. D. Wittman, Tetrahedron Lett., 27, 2443 (1986).
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5) T. Oishi and H. Akita, J. Synth. Org. Chem., 41, 1031 (1983).
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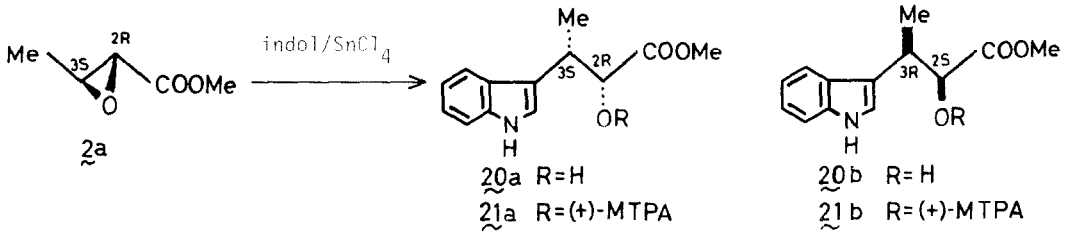
7) Reactions are not optimized yet. Much higher ratio is expected to be obtained by changing base and reaction conditions.
8) Coupling constants across the epoxide (2b, J=2.0 Hz; 2b', J=4.6 Hz) show that the main product 2b is the desired trans epoxide and the minor product, cis-isomer 2b'.
9) Satisfactory analytical data were obtained for all new compounds.
10) Absolute structure and optical purity were determined as follow: 2a [(bp 70-73°C/26 mmHg,

$[\alpha]_D^{24}$ -22.56° (c=1.52, $CHCl_3$), NMR ($CDCl_3$) δ: 1.405 (d, J=5.1 Hz, 3H; C_3-Me), 3.205 (d, J=2.0 Hz, 1H; C_2-H), 3.242 (dq, J=2.0, 5.1 Hz, 1H; C_3-H), 3.780 (s, 3H; COOMe)], after purification as a brucine salt, was converted into (2R,3S)-indolmycenic methyl ester 20a[9] ($[\alpha]_D^{25}$ -4.62° (c=1.56, MeOH)) by the known procedure,[11] whose spectral data were in agreement with those of an authentic (2S,3R)-20b ($[\alpha]_D^{24}$ +4.3° c=0.93, MeOH, corresponding to 93% e.e.)[12] except for the sign of $[\alpha]_D$. Therefore, 20a and thence 2a, were found to possess 2R, 3S-configuration. In order to determine optical purity of 20a, 20a was converted into (+)-MTPA ester 21a (δ: 3.763, s, 3H; COOMe). 21a was found to be optically pure (>99% e.e.) from the NMR (400 MHz) data. (cf. 21b; δ: 3.806, s, 3H; COOMe)



11) M. Schach von Wittenau and H. Els, J. Am. Chem. Soc., 83, 4678 (1961), 85, 3425 (1963).

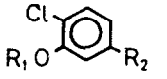
12) T. Takeda and T. Mukaiyama, Chemistry Lett., 1980, 163.

13) 8; $[\alpha]_D^{25}$ -23.32° (c=5, $CHCl_3$), NMR ($CDCl_3$) δ: 1.210 (d, J=7.1 Hz, 3H; sec-Me), 2.163 (d, J=2.5 Hz, 1H; acetylenic H), 3.100 (d, J=6.4 Hz, 1H; OH), 3.820 (s, 3H; COOMe), 4.270 (dd, J=4.0, 6.4 Hz, 1H; CHOH)

14) 10; NMR ($CDCl_3$) δ: 1.067 (d, J=6.8 Hz, 3H; sec-Me), 3.387 (s, 3H; OMe), 3.749 (s, 3H; COOMe)

15) 12; $[\alpha]_D^{21}$ +19.34° (c=5, $CHCl_3$), IR (CCl_4): 1755, 1740 (sh) cm^{-1}, NMR ($CDCl_3$) δ: 0.904 (d, J=7.1 Hz, 3H; sec-Me), 3.388 (s, 3H; OMe), 3.760 (s, 3H; COOMe), 3.711 (d, J=3.9 Hz, 1H; CHOMe)

16) Methylation (Me_2SO_4/K_2CO_3) of the chlorophenol 22 followed by oxidation with $KMnO_4$ gave carboxylic acid 23 in 49% yield. Reduction of 23 with $LiAlH_4$ in THF and the subsequent PBr_3 treatment provided bromo compound 24 in quantitative yield. Refluxing of 24 with triphenylphosphine in benzene provided phosphonium salt 14 in 76% yield.



22 R_1=H R_2=Me 24 R_1=Me R_2=CH_2Br

23 R_1=Me R_2=COOH 14 R_1=Me R_2=$CH_2\overset{+}{P}Ph_3\,Br^-$

17) cis-17; $[\alpha]_D^{21}$ +74.90° (c=5.1, $CHCl_3$), IR (CCl_4): 3440, 3630 cm^{-1}, NMR ($CDCl_3$) δ: 0.953 (d, J=6.5 Hz, 3H; C_{10}-Me), 3.213 (s, 3H; C_9-OMe), 3.898 (s, 3H; C_2-OMe), 5.661 (dd, J=9.8, 12.0 Hz, 1H; C_8-H), 6.733 (d, J=12.0 Hz, 1H; C_7-H), trans-18; $[\alpha]_D^{21}$ +31.03° (c=4.18, $CHCl_3$), IR (CCl_4): 3440, 3630 cm^{-1}, NMR ($CDCl_3$) δ: 0.963 (d, J=6.5 Hz, 3H; C_{10}-Me), 3.337 (s, 3H; C_9-OMe), 3.927 (s, 3H; C_2-OMe), 6.060 (dd, J=15.9, 7.2 Hz, 1H; C_8-H), 6.524 (d, J=15.9 Hz, 1H; C_7-H)

18) 19; $[\alpha]_D^{20.5}$ +10.23° (c=3.1, $CHCl_3$), IR (CCl_4): 1735 cm^{-1}, NMR ($CDCl_3$) δ: 1.001 (d, J=6.8 Hz, 3H; C_{10}-Me), 2.264-2.330 (m, 1H; C_{10}-H), 3.316 (s, 3H; C_9-OMe), 3.594 (dd, J=5.3, 7.6 Hz, 1H; C_9-H), 3.641 (s, 3H; COOMe), 3.929 (s, 3H; C_2-OMe), 6.041 (dd, J=7.6, 15.9 Hz, 1H; C_8-H), 6.496 (d, J=15.9 Hz, 1H; C_7-H)

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