Tetrahedron Letters,Vol.29,No.49,pp 6449-6452,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

DETERMINATION OF ABSOLUTE STRUCTURE OF C_{16}-C_{22} PART OF IRUMAMYCIN. CHIRAL SYNTHESIS OF DEGRADATION PRODUCT

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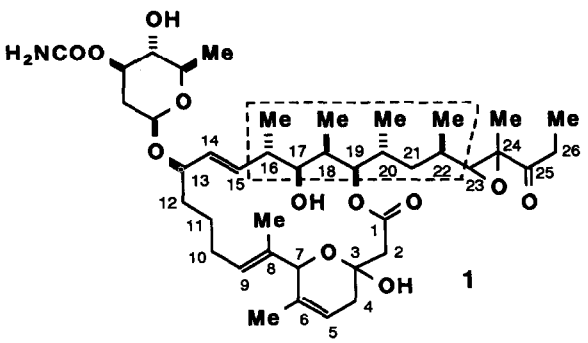
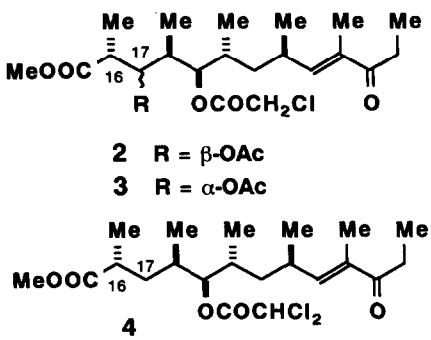
Summary; Absolute structure of C_{16}-C_{22} part of Irumamycin (1) was determined by comparing the degradation product 2 with the synthetic (+)-2.

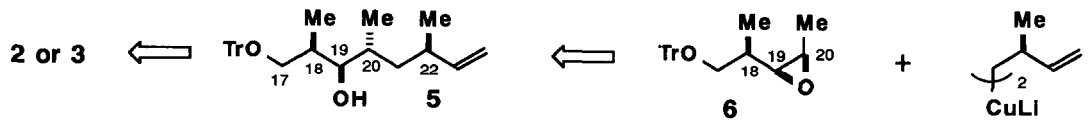
Irumamycin (1) is an antibiotic found in a culture broth of Streptomyces subflavus subsp. irumaensis subsp. nov. AM-3603 and exhibits high activity against phytopathogenic fungi.[1] Although the gross structure has been deduced by spectroscopic and chemical methods,[2] the stereochemistry of its aglycon part remains unknown. We now report that the stereostructure of the C_{16}-C_{22} part of irumamycin was determined as shown in 1 by comparing the degradation product derived from 1 with (+)-2 synthesized by authenticated methods.

The relative and absolute stereostructure of the reported degradation product of 1 is suspected to be shown as either 2 or its $C_{17\alpha}$-acetoxyisomer 3, since the degradation product of venturicidin[3] whose aglycon corresponds to 17-deoxyirumanolide II[4] has been established as 4. Thus, stereoselective syntheses of both optically active esters, 2 and 3, were examined.



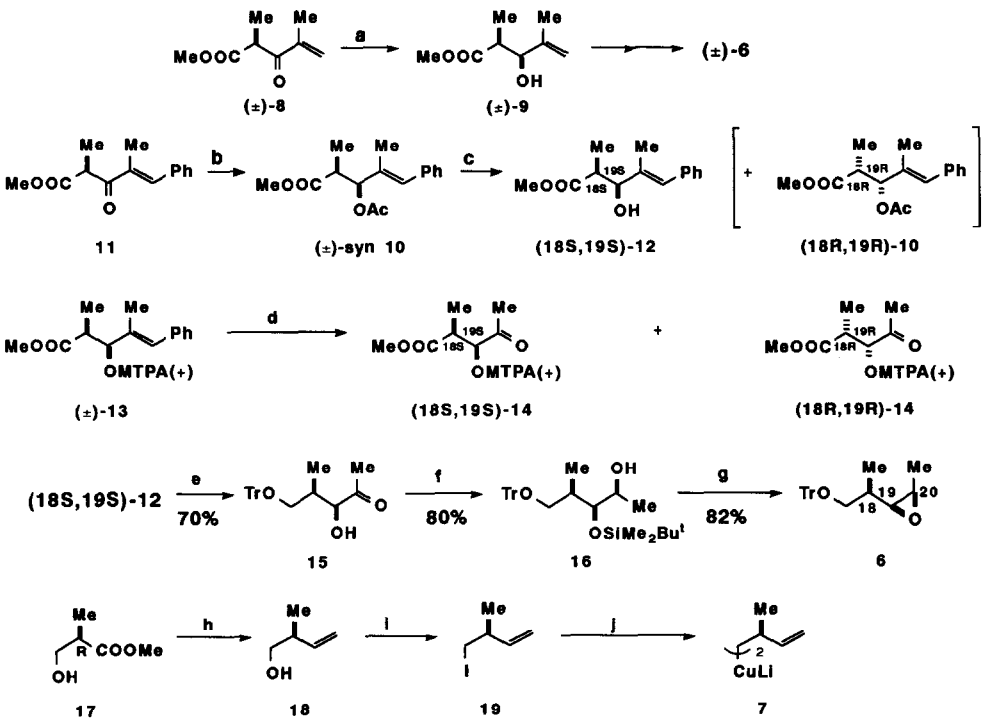


Retrosynthetic analysis of 2 or 3 reveals that 5 could be a precursor. Introduction of two chiral centers at the left-hand side of 5 is expected to be achieved by applying the known procedure. Compound 5 can be obtained from epoxide 6 and cuprate reagent 7.



Since we have already synthesized the racemate 6[5] starting from (±)-8 via (±)-9, the initial requirement is to synthesize the optically active 9. We reported earlier the kinetic resolution of the acetate of (±)-9 with lipase Amano A-6 isolated from Aspergillus

niger giving (18S,19S)-9, but optical purity was 80% e.e.[6] This difficulty could be overcome by slightly modifying the structure of the substrate. In fact, lipase (Amano A-6) catalyzed hydrolysis of (±)-syn 10[7] affords alcohol 12 ($[\alpha]_D^{23}$ -23.8° (c=5.0, $CHCl_3$), 35% yield) in high optical yield (96% e.e.) along with the unchanged acetate 10 ($[\alpha]_D^{23}$ -8.3° (c=5.0, $CHCl_3$), 62% e.e., 56% yield).[8] The optical purities of (-)-12 and (-)-10 were calculated based on NMR (400 MHz) data of the corresponding (+)-MTPA esters ((+)-MTPA ester from (-)-12, δ 3.66, COOMe; (+)-MTPA ester from (-)-10, δ 3.64, COOMe). The absolute structure of (-)-12 was determined as follows. Ozonolysis of (±)-syn 13 prepared from 11[7] affords a mixture of ketones 14. Two singlets due to methoxycarbonyl group appear at δ 3.70 and δ 3.60. Since the signal appearing at δ 3.60 corresponds to that of the authentic (18R,19R)-14[6], the signal appearing at δ 3.70 should be assigned as that of (18S,19S)-14. Ozonolysis of (+)-MTPA ester of (-)-12 affords ketone 14. Its methoxycarbonyl group appears at δ 3.70, which clearly shows that the product 14, consequently (-)-12, should possess (18S,19S)-configurations. Alcohol 12 was converted into ketone 15 in three steps (1. $LiAlH_4$, 2. selective tritylation, 3. ozonolysis), which was then transformed into the optically active epoxide 6 ($[\alpha]_D^{26.5}$ +3.7° (c=1.27, $CHCl_3$)) via 16 as described in the conversion of the corresponding racemate[5] (1. ^{t}butyldimethylsilylation followed by stereoselective reduction with $NaAlH_2(OCH_2CH_2OMe)_2$ giving syn-product 16, 2. mesylation

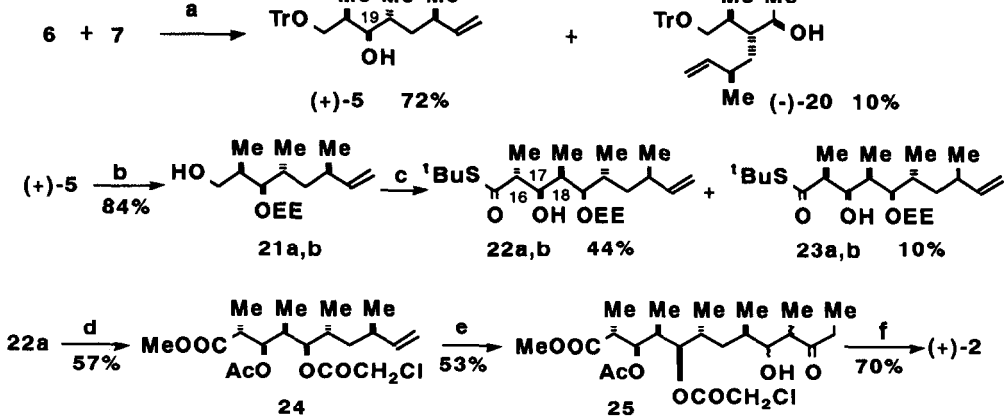


a; $Zn(BH_4)_2$, b; 1)$Zn(BH_4)_2/CH_2Cl_2$ 2)Ac_2O/Pyridine c; lipase/0.1 M phosphate buffer (pH 7.25), 33°C
d; O_3/Me_2S e; 1)$LiAlH_4$ 2)TrCl/Pyridine/DMAP 3)O_3/Me_2S f; 1)^t$BuMe_2SiCl$/Imidazole/DMF
2)$NaAlH_2(OCH_2CH_2OMe)_2$ g; 1)MsCl/Pyridine 2)$Bu_4N^+F^-\cdot 3H_2O$/THF h; 1)DHP/PPTS 2)$LiAlH_4$
3)$(COCl)_2$/DMSO/Et_3N 4)$Ph_3P^+MeBr^-$/n-BuLi 5)p-TsOH·H_2O/EtOH i; 1)MsCl/Et_3N 2)NaI/acetone
j; 1)^{t}BuLi, -100°C 2)CuI, -65°C

followed by desilylation with $Bu_4N^+F^-$ and the concomitant epoxidation). Iodide 19, a precursor for the chiral cuprate 7 was synthesized from the commercially available chiral synthon 17. Conversion of the carbomethoxyl group of 17 to the vinyl group was achieved following Kishi's procedure[9] (five steps, 26% overall yields). Mesylation of the resulting 18 and the subsequent NaI treatment led to iodide 19 ($[\alpha]_D^{20}$ -11° (c=1.18, $CHCl_3$)) in 75% overall yield.

The crucial coupling reaction between the disubstituted epoxide 6 and the α-branched chiral cuprate 7 derived from 19 (1. ^tBuLi, 2. CuI in Et_2O at -65°C) was then examined. Addition of $BF_3.Et_2O$[10] was required for the initiation of the reaction and attack of 7 was found to take place mainly at the less hindered C_{20} side of the epoxide of 6, as expected, producing 5 (72% yield, $[\alpha]_D^{20}$ +19.6° (c=1.0, $CHCl_3$)) along with a small amount of the regio isomer 20 (10% yield, $[\alpha]_D^{20}$ -23.7° (c=0.77, $CHCl_3$)).

Now that a central part of 2 involving four chiral centers was constructed, elongation of the carbon chain to both sides of 5 was undertaken. Protection of C_{19}-OH with ethyl vinyl ether and the subsequent removal of trityl group from (+)-5 with Na in liq. NH_3 provided a 1:1 mixture of 21a and 21b, isomers due to the ethoxyethyl group, in 84% yield. After separation of the mixture by SiO_2 chromatography, one of the isomers 21a was oxidized with PDC and then condensed with ^{t}butylthiopropionate in the presence of LDA to yield the 16,17-anti-17,18-syn-22a (44%)[11] along with the 16,17-syn-17,18-syn-23a (10%).[11] Conversion of the thioester group of 22a into the methoxycarbonyl group, acetylation of C_{17}-OH, deethoxyethyl group and subsequent chloroacetylation provided (+)-24 ($[\alpha]_D^{22}$ +9.4° (c=0.78, $CHCl_3$)) in 57% overall yield. Another ethoxyethyl ether 21b was also converted into (+)-24 in the same way as 21a. Ozonolysis of (+)-24 and the subsequent condensation of the liberated aldehyde with diethylketone in the presence of LDA yielded aldol product 25 in 53% yield. Finally, dehydration of 25 afforded (+)-enone 2 ($[\alpha]_D^{20}$ +13.8° (c=0.8 $CHCl_3$)) in 70 % yield.[12] Physical data ($[\alpha]_D$, 400 MHz NMR, IR, UV) of the synthetic (+)-2 were identical with those of



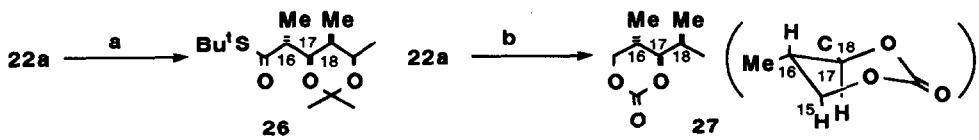
a; BF_3·Et_2O, -65°C b; 1)EtO⟋/PPTS 2)Na/liq.NH_3 c; 1)PDC/Zeolite A 3 2)EtCOSBu^t/LDA d; 1)Na_2CO_3/MeOH 2)Ac_2O/DMAP/Pyridine 3)5% aq.AcOH/MeOH (1:1) 4) $(ClCH_2CO)_2O$/Pyridine e; 1)O_3/Me_2S 2)Et_2CO/LDA f; p-TsOH·H_2O/$CaCl_2$/acetone

the degradation product 2 ($[\alpha]_D^{20}$ +14.3° (c=0.7, $CHCl_3$)) derived from the natural product. The absolute structure of the C_{16}-C_{22} part of natural Irumamycin (1) was thus established as shown in 1.

Acknowledgements: The authors are grateful to Professor S. Ōmura (Kitasato University) for providing an authentic sample of the degradation product from natural product and its spectral data. Thanks are also due to Amano Pharmaceutical Co., Ltd. for providing lipase, and to Kanegafuchi Chemical Industry Co., Ltd. for their supply of pure methyl (R)-β-hydroxy-isobutyrate 17. This work was supported by the Life Science Research Project of this Institute.

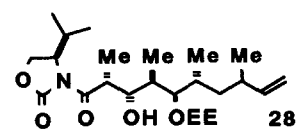
References and Notes

1) S. Ōmura, Y. Tanaka, A. Nakagawa, Y. Iwai, M. Inoue, H. Tanaka, J. Antibiotics, 35, 256 (1982).
2) S. Ōmura, A. Nakagawa, Y. Tanaka, J. Org. Chem., 47, 5413 (1982).
3) M. Brufani, L. Cellai, C. Musu and W. Keller-Schierlein, Helv. Chim. Acta, 55, 2329 (1972).
4) N. Sadakane, Y. Tanaka, S. Ōmura, J. Antibiotics, 36, 931 (1983).
5) T. Nakata, M. Fukui, H. Ohtsuka and T. Oishi, Tetrahedron, 40, 2225 (1984).
6) H. Akita, H. Matsukura and T. Oishi, Tetrahedron Lett., 27, 5241 (1986).
7) Compound 10 was prepared from the corresponding β-keto ester 11 by $Zn(BH_4)_2$ reduction (syn : anti = 16:1; 92% combined yield) followed by acetylation. In the kinetic hydrolysis of the related phenyl-involving substrate, a significant increase of the optical purity of the product has already been observed.[6]
8) Satisfactory analytical data were obtained for all new compounds.
9) T. Nakata and Y. Kishi, Tetrahedron Lett., 2745 (1978).
10) a) A. Ghribi, A. Alexakis, J. F. Normant, Tetrahedron Lett., 25, 3075 (1984).
b) B. H. Lipshutz, D. A. Parker, J. A. Kozlowski, S. L. Nguyen, ibid., 25, 5959 (1984).
11) The relative configuration at the C_{16}-C_{18} positions was determined as follows: The coupling constant between C_{17} and C_{18} protons of the isopropylidene derivative 26 derived from 22a was small ($J_{17,18}$=2.1 Hz), which supports the 17,18-syn structure. The 16,17-anti structure of 22a was determined by the large coupling constant ($J_{16,17}$=9.9 Hz) due to the diaxial relationship of C_{16}-H and C_{17}-H in the cyclic carbonate 27 derived from 22a. The 17,18-syn structure of 23a was determined from the small coupling constant (1.9 Hz) between C_{17} and C_{18} protons of the isopropylidene derivative from 23a.



a; 1)10% AcOH-H_2O/THF/MeOH (1:1:1) 2)$Me_2C(OMe)_2$/CSA
b; 1)Na_2CO_3/MeOH 2)$LiAlH_4$ 3)Im_2CO/PhH 4)PPTS/MeOH/THF

12) The corresponding $C_{17\alpha}$-OAc isomer 3 was also synthesized from 28 prepared from (±)-5 using the Evans procedure. The NMR spectrum (400 MHz) of 3 was found to be clearly different from that of 2.



(Received in Japan 9 September 1988)