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Syntheses of (3S, 4R, 15S)-4,15-Dimethyl-1,5-dioxa-3-(3′-formamidosalicylamido)-cyclopentadecane-2,6-dione and Its (15R)-Epimer, New Antimycin Analogs[1]

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A new type of antimycin analogs, (3S, 4R, 15S)-4,15-dimethyl-1,5-dioxa-3-(3′-formamidosalicylamido)-cyclopentadecane-2,6-dione (**10a**) and its (15R)-epimer (**10b**) have been synthesized. The epimeric fifteen-membered amino-dilactone moieties in **10a** and **10b** were synthesized from a masked L-threonine and *t*-butyl DL-10-hydroxyundecanoate. Each of the separated epimeric amino-dilactones was *N*-acylated with *O*-benzyl-3-nitrosalicylic acid *N*-hydroxysuccinimide ester. Hydrogenation followed by *N*-formylation afforded the antifungal substances, **10a** and **10b**. The 10-*C*-configurations of **10a** and **10b** were determined as "S" and "R", respectively. The (15S)-epimer (**10a**) showed apparently stronger antifungal activity against *Piricularia oryzae* than that of the (15R)-epimer (**10b**).

Recently the total syntheses of dehexyl-deisovaleryl-oxy-antimycin A_1 as a prototype of antimycin A and of antimycin A_3 in a form of the diastereoisomeric mixture have been reported from our laboratory.[2,3]

The most striking characteristic of the structure of antimycin A is its nine-membered dilactone ring linked *via* an amide linkage to 3-formamidosalicylic acid.[4] We now wish to report the syntheses of a new type of antimycin analogs (**10a**) and its epimer (**10b**) which have a fifteen-membered dilactone ring instead of nine-membered ring in antimycin A.

t-Butyl 10-oxoundecanoate (**2**) was prepared from 10-oxoundecanoic acid (**1**)[5] and isobutene by the

1) Part XLI of "Studies on Antibiotics and Related Substances" by Sumio Umezawa.

2) M. Kinoshita and S. Umezawa, This Bulletin, **42**, 854 (1969); *ibid.*, **43**, 897 (1970).

3) M. Kinoshita, M. Wada, and S. Umezawa, *J. Antibiot.* (Tokyo), **22** (11), 580 (1969).

4) F. M. Strong, J. P. Dickie, M. E. Loomans, E. E. van Tamelen, and R. S. Dewey, *J. Amer. Chem. Soc.*, **82**, 1514 (1960). E. E. van Tamelen, J. P. Dickie, M. E. Loomans, R. S. Dewey, and F. M. Strong, *ibid.*, **83**, 1639 (1961).

5) J. Cason, *ibid.*, **68**, 2078 (1946).

same method as previously reported[2] in an 83% yield. Sodium borohydride reduction of **2** in tetrahydrofuran afforded *t*-butyl DL-10-hydroxyundecanoate (**3**) in a 95.8% yield. Catalytic hydrogenation of **2** with Raney Ni W-5 in ethanol also gave 3, however, the yield in this process was low (57.1%).

$CH_3—CO—(CH_2)_8—CO_2R$

1: R=H

2: R=*t*-Bu

↓

$CH_3-CH(OH)-(CH_2)_8-CO_2-Bu^t$

3

↓

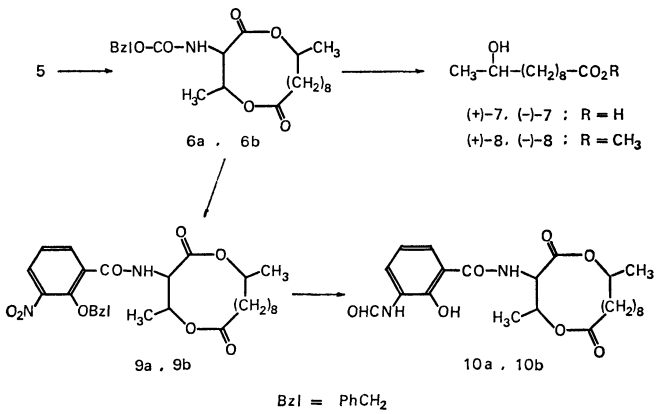
$CH_3-CH(OR)-CH(NHCOOCH_2Ph)-CO-O-CH(CH_3)-(CH_2)_8-CO_2R$

4: R=*t*-Bu

5: R=H

The racemic *t*-butyl 10-hydroxyundecanoate (**3**) was allowed to react with excess amount of *N*-benzyloxycarbonyl-*O*-*t*-butyl-L-threonine[6] in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCCI) and pyridine in ether. The condensation product was purified by silica gel column chromatography with a petroleum ether - diisopropyl ether (2 : 1) system to afford *t*-butyl 10-(*N*-benzyloxycarbonyl-*O*-*t*-butyl-L-threonyloxy)undecanoate (**4**) as a diastereomeric mixture in a 63.5% yield.

De-*t*-butylation of **4** with trifluoroacetic acid gave a free linear ester acid (**5**) which was cyclized in 0.04 M benzene solution by adding 2 moles of trifluoroacetic anhydride at 70°C for 23 hr. The reaction mixture was concentrated and chromatographed on silica gel with a benzene-butanone (30 : 1) system to give from the first and second peaks crystalline cyclization products, **6a** and **6b** in 18.2 and 17.5%, respectively. The products, **6a** and **6b** were found to be the diastereomeric intramolecular cyclization products, namely, the single 15-*C*-epimers of (3S, 4R)-3-(benzyloxycarboxamido)-4,15-dimethyl-1,5-dioxacyclopentadecane-2,6-dione on the basis of elemental analyses, NMR, IR spectra, and molecular weight determinations by mass spectra.



6) E. Schröder, *Ann. Chem.*, **670**, 127 (1963).

The absolute configurations of 15-C-atoms in the epimeric dilactone compounds, **6a** and **6b** were determined as "S" and "R", respectively, by application of Horeau's method[7] to the optical active methyl 10-hydroxyundecanoate, (+)-**8** and (−)-**8**, which were obtained by diazomethane treatment of the crystalline enantiomers, 10-hydroxyundecanoic acids, (+)-**7** and (−)-**7**, derived from **6a** and **6b**, respectively, by the hydrolysis with methanolic sodium hydroxide solution.

The benzyloxycarbonyl groups of **6a** and **6b** were removed by catalytic hydrogenolysis over palladium black in methanol to give the corresponding free amino-dilactones, which were directly *N*-acylated with an active ester, *O*-benzyl-3-nitrosalicylic acid *N*-hydroxysuccinimide ester[2] in tetrahydrofuran.
The crude *N*-acylation products were purified through silica gel columns with a *n*-hexane-ethyl acetate (2 : 1) system to afford the corresponding (3S,4R,15S)-4,15-dimethyl-1,5-dioxa-3-(*O*-benzyl-3′-nitrosalicylamido)-cyclopentadecane-2,6-dione (**9a**) and its (15R) epimer (**9b**) as glassy solids in 89.2 and 86.1% yield, respectively. The structures of **9a** and **9b** were confirmed by their NMR spectra (Table 1).

The compounds, **9a** and **9b** were then hydrogenolyzed over palladium black in methanol to yield the corresponding *N*-(3′-aminosalicyloyl)amidodilactones, which were immediately *N*-formylated with 98% formic acid and DCCI. The crude products were purified by preparative thin-layer chromatography with a *n*-hexane-ethyl acetate (2 : 1) system to afford the title compounds, (3S, 4R, 15S)-4,15-dimethyl-1,5-dioxa-3-(3′-formamidosalicylamido)-cyclopentadecane-2,6-dione (**10a**)(as a crystal) and its (15R)-epimer (**10b**)(as a glassy solid), in 44.7 and 50.7% yield, respectively.

The UV-absorptions of **10a** and **10b** were very similar to those of natural antimycin A and dehexyl-deisovaleryloxy-antimycin A_1. The IR-spectra were also similar to those of the natural product and the analog in respect to the characteristic absorptions assignable to ester carbonyl, formamido and aromatic amido groups.

The structures of **10a** and **10b** were further confirmed by the inspection of their NMR spectra (Table 1).

The coupling constants ($J_{3,4}$=2.0) observed in the NMR spectra of the dilactone compounds, **6a**, **6b**, **9a**, **9b**, **10a**, and **10b** (Table 1) are consistent with the partial conformation in which the vicinal threonine-protons, 3–H and 4–H of the fifteen-membered dilactone ring are *gauche*-related. It has recently been reported that in neoantimycin,[8] the vicinal threonine-protons of the fifteen-membered tetralactone ring have a small coupling constant (J=2.5 Hz), similar to that of the dilactone compounds as described above.

Bioassay. The synthetic new antimycin analogs, **10a** and **10b** showed strong inhibition against certain fungi. Minimal inhibitory concentrations

7) A. Horeau, *Tetrahedron Lett.*, **1961**, 506; *ibid.*, **1962**, 965.
8) L. Caglioti, D. Misiti, R. Mondelli, A. Selva, F. Arcamone, and G. Cassinelli, *Tetrahedron*, **25**, 2193 (1969).

Table 1. 60MHz-NMR-spectra of the amino-dilactones
[Splittings,[a] δ(ppm),[b] J(Hz)[c]]

Compounds Protons	6a	6b	9a	9b	10a	10b
15-CH_3	d. 1.22 (6.2)	d. 1.18 (6.2)	d. 1.27 (?)	d. 1.18 (6.2)	d. 1.27 (6.2)	d. 1.24 (6.2)
4-CH_3	d. 1.33 (6.5)	d. 1.31 (6.5)	d. 1.27 (6.5)	d. 1.24 (6.5)	d. 1.36 (6.5)	d. 1.34 (6.5)
3-H	dd. 4.48 (10.0/2.0)	dd. 4.41 (10.0/2.0)	dd. 5.01 (9.5/2.0)	dd. 5.01 (9.5/2.0)	dd. 5.00 (9.5/2.0)	dd. 5.00 (9.5/2.0)
15-H	m. 4.9—5.4	m. 4.8—5.3	m. 5.0—5.4	m. 5.0—5.4	tq. 5.23 (6.2)	m. 4.95—5.35
Ph-CH_2	s. 5.18	s. 5.20	dd. 5.23	dd. 5.28		
4-H	dq. 5.42 (6.5/2.0)	dq. 5.64 (6.5/2.0)	dq. 5.57 (6.5/2.0)	dq. 5.66 (6.5/2.0)	dq. 5.53 (6.5/2.0)	dq. 5.78 (6.5/2.0)
5'-H(Ar)			t. 7.40 (8.0/8.0)	t. 7.40 (8.0/8.0)	t. 6.95 (8.0/8.0)	t. 7.00 (8.0/8.0)
NH(Thr)	d. 5.60 (10.0)	d. 5.30 (10.0)	d. 8.23 (9.5)	d. 7.93 (9.5)	d. 7.13 (9.5)	d. 7.02 (9.5)
4'-H(Ar)			dd. 7.98 (8.0/2.0)	dd. 7.98 (8.0/2.0)	dd. 7.38 (8.0/1.9)	dd. 7.31 (8.0/1.9)
ArNHCHO					s. 7.99	s. 8.13
ArNHCHO					s. 8.56	s. 8.58
6'-H(Ar)			dd. 8.33 (8.0/2.0)	dd. 8.38 (8.0/2.0)	dd. 8.62 (8.0/1.9)	dd. 8.64 (8.0/1.9)
OH(Ar)					s. 12.76	s. 12.76

a) d., doublet; dd., doublet-doublet; m., multiplet; s., singlet; dq., doublet-quartet; t., triplet; tq., triplet-quartet.
b) Internal standard TMS in *ca.* 10% deuteriochloroform solution.
c) In parentheses.

(mcg/ml) of **10a** and **10b** against *Piricularia orizae* were 1.2×10^{-2} and 12.5, respectively.

It is noteworthy that the configurational or conformational difference between the epimeric dilactone structures of **10a** and **10b** may apparently reflect on the striking difference between their antifungal activities.

Experimental

Melting points were determined on a micro hot stage and were uncorrected. Thin-layer chromatography (TLC) was conducted by the use of WAKOGEL B-5 (Wako Pure Chemical Industries, Ltd.). Silica gel column chromatography was carried out by using WAKOGEL C-200 which was activated at 110°C for 1 hr. IR-spectra were recorded on a Hitachi IPI-2 spectrometer, UV-spectra were taken in a Hitachi Perkin-Elmer UV-VIS spectrometer 139. NMR spectra were recorded on a Varian-A-60D spectrometer (TMS as an internal standard) in *ca.* 5—10% (W/V) solution in deuteriochloroform. Optical rotations were measured with a Zeiss Photoelectric Precision Polarimeter 0.005° employing a 0.5 decimeter tube. In general, all concentrations were carried out in a rotary evaporator at reduced pressure below 40°C.

t-*Butyl 10-Oxoundecanoate (2).* To a solution of 10-oxoundecanoic acid (**1**) (11.4 g, mp 55.8—57.0°C) in a mixture of dichloromethane (34 m*l*) and conc. sulfuric acid (0.33 m*l*) was added liquid isobutene (33.4 m*l*) under cooling at −30°C. The stoppered flask was allowed to stand at room temperature for 70 hr. The reaction mixture was processed by the same method as described in the previous paper[2] to give **2** as colorless liquid boiling at 129.5—131°C under 4 mmHg: Yield, 14.6 g (82.8%); n_D^{20} 1.4383; ν_{max}^{liq} 1727 cm^{-1} (C=O and ester).

Found: C, 70.60; H, 11.13%. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01%.

t-*Butyl 10-Hydroxyundecanoate (3).* Sodium borohydride (343 mg, 9.08 mmol) was added to a solution of *t*-butyl 10-oxoundecanoate (**2**) (582 mg, 2.27 mmol) in dry tetrahydrofuran (19.3 m*l*) and stirred for 3 hr at room temperature. The reaction mixture was neutralized with 20% H_2SO_4 (1.0 m*l*) and extracted with ether. The combined extracts were washed with $NaHCO_3$ and saturated NaCl solution. After evaporation of the solvent, the residue was distilled under reduced pressure. The fraction boiling at 114—116.5°C/0.03 mmHg was collected: yield, 568 mg (95.8%); n_D^{20} 1.4428; ν_{max}^{liq} 3440 (OH) and 1735 cm^{-1} (ester).

Found: C, 69.40; H, 11.75%. Calcd for $C_{15}H_{30}O_3$: C, 69.72; H, 11.70%.

t-*Butyl 10-*(N-*Benzyloxycarbonyl*-O-t-*butyl*-L-*threonyloxy*)*undecanoate (4).* A solution of *N*-benzyloxycarbonyl-*O*-*t*-butyl-L-threonine (6.00 g, 19.4 mmol) in dry ether (13.1 m*l*) was added dropwise during 40 min to a stirred solution of *t*-butyl 10-hydroxyundecanoate (**3**)(5.00 g, 19.4 mmol), DCCI (4.41 g, 21.4 mmol) and dry pyridine (1.65 m*l*, 19.4 mmol) in dry ether (20 m*l*) cooled to 0°C. Stirring at 0°C was continued for a further 4 hr. After standing at 0°C for 20 hr, to the reaction mixture, DCCI(2.2 g) and dry pyridine(0.83 ml) and then a solution of *N*-benzyloxycarbonyl-*O*-*t*-butyl-L-threonine (3.00 g) in dry ether (6 m*l*) was dropped under stirring at 0°C. Further additions of the threonine derivative (1.0 g×2), DCCI (1.10 g ×2) and dry pyridine (0.413 m*l*×2) in two portions were undertaken in the same procedure as in the preceding additions in 24-hr intervals. After standing at 0°C for 20 hr the precipitate of *N*,*N*'-dicyclohexylurea (5.16 g, 53.7%) was filtered off and the filtrate was treated with acetic acid (1.5 m*l*) under stirring at 0°C for 2 hr. An additional

urea was removed by filtration and the filtrate was washed with 5% $NaHCO_3$ solution, 5% citric acid and saturated NaCl solution, dried over Na_2SO_4, and concentrated to dryness. The syrupy residue (17.31 g) was chromatographed on a silica gel column (1.78 kg, 8.2×65 cm). Elution with a petroleum ether-diisopropyl ether (2 : 1) system gave a straw-colored syrup (6.77 g, 63.5%) as a first fraction which behaved as a homogeneous compound on the tlc using the same solvent system as in the column chromatography: $[\alpha]_D^{23.5}$ −2.5° (*c* 1.63, chloroform); ν_{max}^{liq} 3460, 3360 (NH), 1730 (ester and amide I) and 1505 cm^{-1} (amide II).

Found: C, 68.07; H, 9.40; N, 2.70%. Calcd for $C_{31}H_{51}O_7N$: C, 67.73; H, 9.35; N, 2.55%.

*10-(N-Benzyloxycarbonyl-L-threonyloxy)undecanoic Acid (**5**).* A mixture of **4** (1.72 g) and trifluoroacetic acid (19 ml) was kept at room temperature with occasional swirling for 5 min, after which the reaction mixture was evaporated below 10°C. The residual syrup was then dissolved in ether and again evaporated. This procedure was repeated three times to remove trifluoroacetic acid. The final residue was dried over sodium hydroxide under reduced pressure to afford **5** (1.37 g).

*(3S,4R,15S)-3-Benzyloxycarboxamido-4,15-dimethyl-1,5-dioxacyclopentadecane-2,6-dione (**6a**) and (3S,4R,15R)-3-Benzyloxycarboxamido-4,15-dimethyl-1,5-dioxacyclopentadecane-2,6-dione (**6b**).* A mixture of **5** (1.37 g, 3.13 mmol), dry benzene (78 m*l*) and trifluoroacetic anhydride (0.436 m*l*, 3.13 mmol) was heated at 70°C for 14 hr, after which additional trifluoroacetic anhydride (0.436 m*l*) was added and again heated at the same temperature for 9 hr. The reaction mixture was evaporated and the residue was then dissolved in ether and again evaporated. This procedure was repeated three times to remove trifluoroacetic acid. The final residue was dried over sodium hydroxide in a vacuum to yield a crystalline mass (1.65 g). The product was chromatographed on a silica gel column (400 g, 4.7×53 cm) with benzene-butanone (30 : 1) system to give two fractions corresponding to the first and second elution peaks of the chromatogram. The first fraction gave a crystalline cyclization product **6a** (238 mg, 18.2%); mp 69.7—71.2°C (from ethyl acetate-petroleum ether); $[\alpha]_D^{22}$ +7.1° (*c* 1.7, chloroform); ν_{max}^{KBr} 3440 (NH), 1743 (ester), 1725 (amide I) and 1517 cm^{-1} (amide II).

Found: C, 65.68; H, 7.67; N, 3.44%; M (mass spectrometry), 419.2256; M+1, 420.2311. Calcd for $C_{23}H_{33}O_6N$: C, 65.85; H, 7.93; N, 3.34%; M, 419.2308; M+1, 420.2386.

The second fraction afforded a crystalline cyclization product **6b** (229 mg, 17.5%); mp 135.0—136.0°C (from ethyl acetate-petroleum ether); $[\alpha]_D^{22}$ −33.8° (*c* 1.8, chloroform); ν_{max}^{KBr} 3350 (NH), 1740 (ester), 1715 (amide I), and 1535 cm^{-1} (amide II).

Found: C, 66.16; H, 8.31; N, 3.49%. M (mass spectrometry), 419.2313; M+1, 420.2381. Calcd for $C_{23}H_{33}O_6N$: C, 65.85; H, 7.93; N, 3.34%. M, 419.2308; M+1, 420.2386.

*(+)-10-Hydroxyundecanoic Acid [(+)-**7**].* To a solution of **6a** (100 mg, 0.238 mmol) in methanol (0.48 m*l*) was added 10% aq. NaOH (0.24 m*l*, 0.594 mmol) under ice-cooling and stirred for 4.5 hr at room temperature. The mixture was concentrated, diluted with water and extracted ten times with 1 m*l*-portions of ethyl acetate. The aqueous layer was acidified (pH 4) with 10% H_2SO_4 and extracted with ethyl acetate (1.5 m*l*×4). The dried ethyl acetate layer was evaporated to give a crystalline mass (93.2 mg), which was dissolved in methanol and hydrogenolysed over palladium black.[9] The reduction product was chromatographed on silica gel (6 g) with *n*-hexane-ethyl acetate-acetic acid (20 : 10 : 1) system to afford (+)-**7** (40.9 mg, 85.3%); mp 61.5—63.7°C (from ethyl acetate-petroleum ether); $[\alpha]_D^{21}$ +6.2° (*c* 1.9, chloroform); ν_{max}^{KBr} 3360 (OH), 1712 cm^{-1} (COOH).

Found: C, 65.67; H, 11.12%. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96%.

*(−)-10-Hydroxyundecanoic Acid [(−)-**7**].* Saponification of **6b** with 10% aq. NaOH by the same procedure as that used to obtain (+)-**7** from **6a** afforded (−)-**7**; mp 62.0—63.0°C; $[\alpha]_D^{21.2}$ −7.0° (*c* 2.5, chloroform); IR-spectrum of (−)-**7** was identical with that of its enantiomer (+)-**7**.

Found: C, 65.48; H, 11.15%. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96%.

*Methyl (+)-19-Hydroxyundecanoate [(+)-**7**].* To a solution of (+)-**7** (18.5 mg) in dry ether (0.6 m*l*) was added excess distilled diazomethane in ether. After 15 min the solution was filtered and the filtrate was evaporated to dryness leaving (+)-**8** as a colorless oil (17.8 mg, 90%). tlc [benzene-acetone (15 : 1)] showed a single spot: $[\alpha]_D^{25}$ +5.6° (*c* 1.8, methanol).

*Methyl (−)-10-Hydroxyundecanoate [(−)-**8**].* The diazomethane treatment of (−)-**7**, similar to that of (+)-**7** gave the enantiomeric methyl ester (−)-**8**: $[\alpha]_D^{25}$ −5.8° (*c* 2.5, methanol).

*Determinations of Absolute Configurations of (+)-**8** and (−)-**8** by Horeau Procedure.* a) α-Phenylbutyric anhydride[10] (50.3 mg, 0.165 mmol) was added to (+)-**8** (18.7 mg, 0.083 mmol) in pyridine (0.5 m*l*). After standing for 18 hr at room temperature, water and benzene were added and the mixture was extracted several times with 0.2 N aq. Na_2CO_3. The extracts were washed with ether, acidified with 6 N HCl and extracted with benzene. The benzene extract was washed with water, dried over Na_2SO_4 and concentrated to dryness. The residue (39.2 mg) had IR and NMR spectra identical with those of racemic α-phenylbutyric acid: $[\alpha]_D^{20}$ −5.0°; $[\alpha]_{546}^{20}$ −6.0°; $[\alpha]_{436}^{20}$ −10.5°; $[\alpha]_{365}^{20}$ −17.7° (*c* 1.96, benzene). Since the recovered α-phenylbutyric acid was levorotatory, the hydroxy ester (+)-**8** has the "S" configuration at its asymmetric center. b) By the same procedure as described in a), the reaction of (−)-**8** (25.2mg, 0.117 mmol) with α-phenylbutyric anhydride (71.2 mg, 0.234 mmol) in pyridine gave a recovered sample (41.5 mg) of α-phenylbutyric acid: $[\alpha]_D^{20.5}$ +4.0°; $[\alpha]_{546}^{20.5}$ +5.3°; $[\alpha]_{436}^{20.5}$ +10.4°; $[\alpha]_{365}^{20.5}$ +18.0° (*c* 2.08, benzene). The configuration at carbinol carbon of (−)-**8**, therefore, is estimated as "R".

*(3S,4R,15S)-4,15-Dimethyl-1,5-dioxa-3-(O-benzyl-3'-nitrosalicylamido)cyclopentadecane-2,6-dione (**9a**).* A solution of **6a** (100 mg, 0.239 mmol) in methanol (3.5 m*l*) was stirred with palladium black (*ca.* 9 mg) for 25 min under bubbling with hydrogen. The filtered reduction mixture was evaporated to yield the free amino-dilactone (65 mg) which showed a single ninhydrin positive spot on tlc with a benzene-acetone (20 : 1) system. The free amino-dilactone (65 mg) was dissolved in dry tetrahydrofuran (1.2 m*l*) and *O*-benzyl-3-nitrosalicylic acid *N*-hydroxysuccinimide ester (88.3 mg, 0.239 mmol) was added. The mixture (pH 6) was kept for 4 hr at room temperature, after which it (pH 5) was allowed to stand for 16 hr at 37°C in an incubator. The reaction mixture (pH 4) was adjusted to pH 6 by the addition of triethylamine and again kept at 37°C for 3 hr. The resulting solution was evaporated to afford a yellow syrup (200 mg)

9) By this hydrogenation process the another saponification product of **6a**, namely *N*-benzyloxycarbonyl-L-threonine, was converted to L-threonine which was easily removed from the title compound by a silica gel column.

10) H. Falk and K. Schlog, *Monatsch. Chem.*, **96**, 276 (1965).

which was purified through a silica gel column (20 g, 1.3×43 cm). Elution with a *n*-hexane - ethyl acetate (2 : 1) system gave the title compound **9a** as a yellow glassy solid: yield 115 mg (89.2%); $[\alpha]_D^{23}$ −16.9° (*c* 1.7, chloroform); $\nu_{max}^{CCl_4}$ 3400 (NH), 1746 (ester), and 1680 cm^{-1} (amide I).

Found: C, 64.64; H, 7.16; N, 4.86%. Calcd for $C_{29}H_{36}O_8N_2$: C, 64.43; H, 6.71; N, 5.18%.

*(3S,4R,15R)-4,15-Dimethyl-1,5-dioxa-3-(O-benzyl-3'-nitrosalicylamido)cyclopentadecane-2,6-dione (**9b**).* The title compound (**9b**) was prepared from **6b** by the same procedure as described for the preparation of the epimer (**9a**) as a yellow glassy solid: yield 86.1%; $[\alpha]_D^{22}$ +35.7° (*c* 1.4, chloroform); $\nu_{max}^{CCl_4}$ 3410 (NH), 1748 (ester), and 1680 cm^{-1} (amide I).

Found: C, 64.69; H, 6.77; N, 5.60%. Calcd for $C_{29}H_{36}O_8N_2$: C, 64.43; H, 6.71; N, 5.18%.

*(3S,4R,15S)-4,15-Dimethyl-1,5-dioxa-3-(3'-formamidosalicylamido)cyclopentadecane-2,6-dione(**10a**).* A solution of **9a** (59.6 mg, 0.109 mmol) in methanol (8 m*l*) was stirred with palladium black under bubbling with hydrogen gas for 30 min. The filtered yellow-green reduction mixture was evaporated to give an orange-red glassy solid (43 mg, 93.9%). The product (43 mg, 0.103 mmol) was dissolved in tetrahydrofuran (1.6 m*l*) and to the solution was added DCCI (22.4 mg, 0.109 mmol) and 98% formic acid (5.4 mg) under ice-cooling. After standing for 23 hr in a refrigerator, the reaction mixture was filtered to remove *N,N'*-dicyclohexylurea (14.7 mg, 60.3%). The orange-red filtrate was evaporated and the crude product (64.8 mg) was purified by preparative thin-layer chromatography (three 20×20 cm-plates) with *n*-hexane - ethyl acetate (2 : 1). The strongest fluorescent band was collected and extracted with ether to afford orange crystals which were recrystallized from ether-petroleum ether (30—40°C) to yield colorless needles of **10a**: yield 21.5 mg (44.2%); mp 124—127.6°C; $[\alpha]_D^{21}$ +49° (*c* 1.1, chloroform); λ_{max}^{MeOH} mμ (log ε), 227 (4.55) and 319 (3.78); $\nu_{max}^{CHCl_3}$ 3430, 3390 (NH), 1740 (ester), 1703 (NHCHO), 1647 (ArCONH), 1613, 1593 (Ar–H) and 1532 cm^{-1} (ArCONH).

Found: C, 61.67; H, 7.23; N, 6.34%. Calcd for $C_{23}H_{32}O_7N_2$: C, 61.59; H, 7.19; N, 6.25%.

*(3S,4R,14R)-4,15-Dimethyl-1,5-dioxa-3-(3'-formamidosalicylamido)cyclopentadecane-2,6-dione (**19b**).* By the same procedure as described for the preparation of **10a**, the title compound (**10b**) was prepared from **9b** as a glassy solid: yield 50.7%; $[\alpha]_D^{22}$ +14° (*c* 1.8, chloroform); λ_{max}^{MeOH} mμ (log ε), 227 (4.46) and 319 (3.77); $\nu_{max}^{CHCl_3}$ 3408, 3465 (NH), 1740 (ester), 1707 (NHCHO), 1647 (ArCONH), 1613, 1596 (Ar–H) and 1536 cm^{-1} (ArCONH).

Found: C, 61.32; H, 7.24; N, 5.86%. Calcd for $C_{23}H_{32}O_7N_2$: C, 61.59; H, 7.19; N, 6.25%.

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