SOME ASPECTS FOR 1,3-DIPOLAR CYCLOADDITION REACTION OF NITRILE OXIDE WITH METHYL CROTONATE IN THE SYNTHESIS OF CARBAPENAM ANTIBIOTICS

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Abstract —— 1,3-Dipolar cycloaddition reaction of the nitrile oxides, generated *in situ* from the nitro compounds (6~9) and phenyl isocyanate, with methyl crotonate afforded the corresponding isoxazolines (10~17) in moderate yields. Hydrogenation of 12, 14 and 16 on platinum oxide gave the amino esters (18 and 20) and the lactam (22), respectively. The amino esters (18 and 20) were converted to the β-lactams (23~26) with ethylmagnesium bromide in tetrahydrofuran. Finally, 3,4-bond formation reaction for the mesyloxy derivative (27) of 24 furnished the carbapenam derivative (28) in good yield.

Recent discovery of various carbapenem antibiotics, such as thienamycin[1-3], epi-thienamycin[4], PS-5[5] and olivanic acids[6-11], prompted us to investigate a synthetic pathway for them, because of their unique structures and their attractive biological activities. We have already reported[12,13] the synthesis of thienamycin (1) using the isoxazoline as a starting material, which was prepared by 1,3-dipolar cycloaddition of the nitrile oxide (3) with methyl crotonate.

In continuation of our work on the synthesis of carbapenam or carbapenem, the extension of 1,3-dipolar cycloaddition reaction was further investigated. Intermolecular 1,3-dipolar cycloaddition of the nitrile oxide, generated *in situ* from the corresponding nitro compound, with crotonates gave the regioisomeric mixtures. Moreover, catalytic reduction of the desired isoxazoline on platinum oxide afforded a mixture of stereoisomers. Based on the consideration of these results, an intramolecular 1,3-dipolar cycloaddition reaction was firstly attempted in order to get rid of regioisomeric problem and a reduction of such bicyclic isoxazolines may also increase the stereoselectivity.

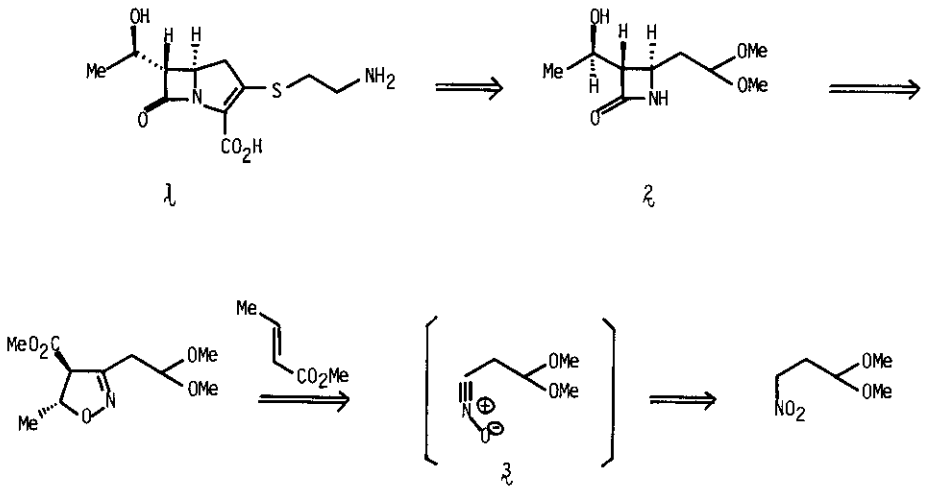


Chart 1

However, the reaction of nitro compounds (4 and 5), prepared from crotonic acid and 3-nitropropan-1-ol[14] or 4-nitrobutan-1-ol[15], with phenyl isocyanate gave no cyclised product, but complicated mixtures. Therefore, our attention turned back to a synthetic route involving intermolecular cycloaddition reaction. More recently, the nitrone-based synthesis of β-lactams has also been reported by Tufariello[16]. Thus, the nitro compounds (6 and 7) were treated with methyl crotonate in the presence of phenyl isocyanate and triethylamine to afford the isoxazolines (10∿13), respectively. Reduction of the desired isoxazoline (12) on platinum oxide under the medium pressure of hydrogen gave the amino ester (18) as a colourless oil, which without separation was converted to the corresponding silylated derivative (19). Treatment of 19 with ethylmagnesium bromide in dry tetrahydrofuran furnished the azetidinones (23 and 24), which have the hydroxyethyl moiety at the C_3-position of β-lactam with R^*-configuration, as previously described[12]. The stereochemistry of these product was easily deduced based on their nmr data [the trans - compound (23) shows C_3-H resonance at 2.83 ppm with J value 2 and 8 Hz, whereas at 3.17 ppm with J value 5 and 9 Hz for the cis-compound (24)]. The major product (24) was then converted with mesyl chloride in pyridine to the mesylate (27), which was then cyclised to carbapenam derivative (28), with retention of the configuration at C_5, C_6 and C_8-position, by treatment with lithium hexamethyl disilazide in 73.9 % yield. The nmr spectrum (δ) of 28 shows the expected resonances at 1.32

(3H, d, J = 6.5 Hz, $CH_3CH(OTMS)$-), 3.28 (1H, dd, J = 5.3 and 9.3 Hz, C_6-H), and 4.02 (1H, dt, J = 6.5 and 9.3 Hz, C_8-H), and its ir spectrum shows no NH and SO_2 absorptions. These spectral data are consistent with the structure 28. Thus, 1,3-dipolar cycloaddition reaction provided a useful pathway for synthesising carbapenams which have 8R*-hydroxyethyl group at the C_6-position. Two other isoxazolines were prepared by 1,3-dipolar cycloaddition reaction to synthesise thienamycin derivatives. The nitro acetal (9), prepared from 4-nitrobutanal[15], was treated with methyl crotonate to give the isoxazolines (14 and 15). Reduction of the desired isomer (14), after separation, gave the amino esters (20). After silylation of 20 with trimethylsilyl chloride and triethylamine, the silylated compound (21) was treated with ethylmagnesium bromide to furnish the separable azetidinones (25 and 26) in 20.16 % and 40.02 % yield. This one-carbon elongated azetidinone (25), compared with 2, may become an important intermediate for carbacephems, such as homothienamycin, and this conversion is now under investigation.

Finally, the five-membered lactam (22) was synthesised from the nitro ester (8) and methyl crotonate by 1,3-dipolar cycloaddition reaction, followed by reduction of isoxazolines (16 and 17). The 4-7 bond formation of the lactam (22) to a carbapenam derivative is also under investigation.

4 n=3
5 n=4

$O_2N-(CH_2)_n-OAc$

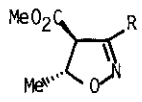
6 n=3
7 n=4

$O_2N-(CH_2)_2CH(CO_2Me)_2$

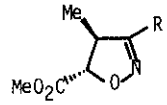
8

$O_2N(CH_2)_3CH$ 

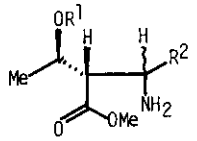
9



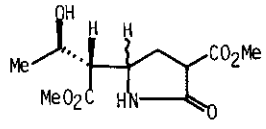
10 R=$(CH_2)_2OAc$
12 R=$(CH_2)_3OAc$
14 R=$(CH_2)_2CH$ 
16 R=$CH_2CH(CO_2Me)_2$



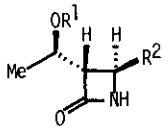
11 R=$(CH_2)_2OAc$
13 R=$(CH_2)_3OAc$
15 R=$(CH_2)_2CH$ 
17 R=$CH_2CH(CO_2Me)_2$



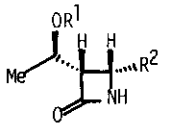
18 R^1=H, R^2=$(CH_2)_3OAc$
19 R^1=$SiMe_3$, R^2=$(CH_2)_3OAc$
20 R^1=H, R^2=$(CH_2)_2CH$ 
21 R^1=$SiMe_3$, R^2=$(CH_2)_2CH$ 



22

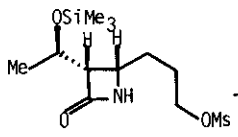


23 R^1=$SiMe_3$, R^2=$(CH_2)_3OH$
25 R^1=H, R^2=$(CH_2)_2CH$ 
29 R^1=H, R^2=$(CH_2)_3OSO_2Me$

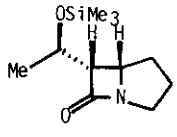


24 R^1=$SiMe_3$, R^2=$(CH_2)_3OH$
26 R^1=H, R^2=$(CH_2)_2CH$
30 R^1=H, R^2=$(CH_2)_3OSO_2Me$

24



27



28

Chart 2

EXPERIMENTAL

3-Nitropropyl Crotonate (4)—— A solution of crotonic acid (2.58 g), a catalytic amount of p-toluenesulfonic acid and 3-nitropropanol[15] (3.15 g) in dry benzene (50 ml) was refluxed with Dean-Stark equipment for 40 h. The mixture was diluted with benzene (50 ml) and washed with saturated sodium hydrogen carbonate solution and dried (Na_2SO_4). Removal of the solvent afforded a colourless oil which was chromatographed on silica gel using benzene as eluant to give the ester (4) (3.87 g) (74.9 %); $\nu_{max.}$ ($CHCl_3$) cm^{-1}: 1720 (C = O), 1550 (NO_2); δ($CDCl_3$): 1.93 (3H, dd, J = 2 and 7 Hz, CH_3-CH=CH), 5.93 (1H, dq, J = 2 and 16 Hz, CH=CH-CO), 7.07 (1H, dq, J = 7 and 16 Hz CH=CH-CH_3); m/e 173 (M^+).

4-Nitrobutyl Crotonate (5)—— A solution of the 4-nitrobutanol[15] (13 g), a catalytic amount of p-toluenesulfonic acid and crotonic acid (11.3 g) in dry dry benzene (150 ml) was refluxed with Dean-Stark equipment for 24 h. After cooling, the benzene layer was washed with saturated sodium hydrogen carbonate solution and water and dried (Na_2SO_4). Evaporation of the solvent gave a brownish oil which was chromatographed on silica gel using benzene as eluant to give the ester (18.6 g) (67 %) as a colourless oil, $\nu_{max.}$ ($CHCl_3$) cm^{-1}: 1710 (C = O), 1540, 1370 (NO_2); δ ($CDCl_3$): 1.86 (3H, d, J = 8 Hz, CH_3-CH=CH), 5.76 (1H, d, J = 15 Hz, CH = CH-CO_2), 6.96 (1H, m, CH_3-CH=CH); m/e 187 (M^+).

3-Nitropropyl Acetate (6)—— Acetyl chloride (25.91 g) was added dropwise to 3-nitropropanol[15] (31.50 g) at 0° with stirring over the period of 3 h. The mixture was extracted with methylene chloride (200 ml) and washed with saturated sodium hydrogen carbonate solution and water, and dried (Na_2SO_4). Evaporation of the solvent gave the acetate (6) (33.25 g) (75.4 %) as a colourless oil which was purified by distillation, b.p. 104 - 110° (10 mmHg); $\nu_{max.}$ ($CHCl_3$) cm^{-1}: 1720 (C = O), 1550 (NO_2); δ($CDCl_3$): 2.10 (3H, s, OAc), 4.29 (2H, t, J = 7 Hz, -CH_2-OAc) 4.58 (2H, t, J = 7 Hz, CH_2NO_2).

4-Nitrobutyl Acetate (7)—— To a stirring solution of silver nitrite (31 g) in dry ether (50 ml) was added a solution of 4-iodobutyl acetate (40 g) in dry ether (100 ml) at 0°. The resulting mixture was further stirred for 8 h at ambient temperature. After filtration and washing of insoluble material with ether, the combined filtrate was concentrated to the residue which was purified by distillation to afford the nitro compound as a pale yellow oil, b.p. 108 - 113° (5 mmHg); $\nu_{max.}$ ($CHCl_3$) cm^{-1}: 1720 (C = O), 1540, 1375 (NO_2); δ (CCl_4): 2.07 (3H, s, OAc), 4.15

(2H, t, J = 6 Hz, $C\underline{H}_2$-OAc), 4.46 (2H, t, J = 6 Hz, $C\underline{H}_2NO_2$).

Dimethyl 2-Nitroethylmalonate (8)—— To a stirred solution of dimethyl malonate (35.7 g) and sodium methoxide [prepared from sodium (6.22 g)] in dry methanol was added 1-bromo-2-nitroethane[17] (41.6 g) dropwise at room temperature. The stirring was further continued for 4 h at room temperature. After removal of the solvent, the residue was treated with water and extracted with ether. The ethereal layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave a reddish oil, which was chromatographed on silica gel using benzene-ethyl acetate (93 : 7 v/v) as eluant to give the malonate (16.2 g) (29.2 %); $\nu_{max.}$ ($CHCl_3$) cm^{-1}: 1730 (C = O); δ ($CDCl_3$): 2.50 (2H, dt, J = 7 Hz, $C\underline{H}_2$-CH_2NO_2), 3.52 (1H, t, J = 7 Hz, $C\underline{H}$ $(CO_2Me)_2$), 3.75 (6H, s, 2 x $OC\underline{H}_3$) 4.48 (2H, t, J = 7 Hz, $C\underline{H}_2NO_2$); m/e 206 (M^+ + 1); Anal. calcd. for $C_7H_{11}NO_6$: C, 40.98; H, 5.40; N, 6.83. Found: C, 41.25; H, 5.47; N, 6.39.

4-Nitrobutanal Ethylene Acetal (9)—— A solution of 4-nitrobutanal[15] (1.5 g), a catalytic amount of p-toluenesulfonic acid and ethylene glycol (1.18 g) in dry benzene was refluxed with Dean-Stark equipment for 20 h. After cooling, the benzene layer was washed with saturated sodium hydrogen carbonate solution and dried (Na_2SO_4). Evaporation of the solvent gave a yellowish oil, which was chromatographed on silica gel using methylene chloride as eluant to afford the acetal (0.95 g) (46.5 %) as a pale yellow oil; $\nu_{max.}$ ($CHCl_3$) cm^{-1}: 1540 (NO_2); δ (CCl_4): 4.93 (1H, t, J = 5 Hz, $C\underline{H}\overset{O}{\underset{O}{\sim}}$). 4.46 (2H, t, J = 7 Hz, $C\underline{H}_2NO_2$), 3.92 br (4H, s, $OC\underline{H}_2C\underline{H}_2O$).

General Procedure for the Preparation of the Isoxazolines (10 ∿ 17)—— To a stirred solution of the nitro compound (0.1 mol equivalent), methyl crotonte (0.12 mol equivalent) and triethylamine (10 ∿ 15 drops) in dry benzene (100 ml) was added phenyl isocyanate (0.25 mol equivalent) in dry benzene (100 ml) under the atmosphere of nitrogen at 0°. After the mixture had been stirred at ambient temperature for 24 h, an insoluble material was filtered off, and the filtrate was washed with water, saturated sodium hydrogen carbonate solution and water, and dried (Na_2SO_4). Evaporation of the solvent gave a yellow oil which was subjected to silica gel column chromatography. Elution with benzene-ethyl acetate (9 : 1 v/v) afforded the desired isoxazoline from the first eluant and the regioisomeric isoxazoline from the second eluant (cf. Table 1).

General Procedure for the Preparation of Amino Esters (18 and 20) and Lactam (22)—— A mixture of the isoxazoline (3 g), platinum oxide (400 mg) and glacial acetic acid (100 ml) was shaken in a current of hydrogen (5 ∿ 6 atm) for 20 h. After filtration and washing of the solid with acetic acid, evaporation of the combined filtrates

gave a pale yellow gum, which was again dissolved in chloroform. The chloroform solution was washed with 10 % NH_4OH and saturated sodium chloride solution, and dried (Na_2SO_4). Evaporation of the solvent afforded the two stereoisomers of the amino ester (18 and 20) or the lactam (22) (cf. Table 2).

Preparation of β-Lactams (23) and (24)—— To a stirred solution of the amino ester (18) (2.7 g) in dry benzene (20 ml) was added triethylamine (2.45 g) and trimethylchlorosilane (2.5 g) in a current of nitrogen at 0°. After the stirring had been continued for 3 h at ambient temperature, the insoluble material was filtered off, and the filtrate was concentrated to give silylated compound (19), which without purification was dissolved in dry tetrahydrofuran. To the above stirred solution was added drop by drop ethylmagnesium bromide (3 mol equivalent) in a current of nitrogen at 0°. After the stirring had further been continued for 8 h at ambient temperature, the mixture was treated with water and extracted with chloroform. The chloroform layer was washed with water and dried (Na_2SO_4). Removal of the solvent gave a colourless oil which was subjected to silica gel column chromatography. Elution with benzene-acetone (8 : 2 v/v) afforded the β-lactam (24) (1.38 g) (51 %); $\nu_{max.}$ ($CHCl_3$) cm^{-1}: 3410 (NH), 1750 (C = O); δ ($CDCl_3$): 0.13 (9H, s, ($C\underline{H}_3)_3Si$), 1.34 (3H, d, J = 6.5 Hz, $C\underline{H}_3$), 3.17 (1H, dd, J = 5 and 9 Hz, C_3-$\underline{H}$) 3.69 (2H, t, J = 6 Hz, $C\underline{H}_2$-OH) 4.29 (1H, m, $CH_3C\underline{H}$(OH)-), 6.58 br (1H, s, $N\underline{H}$); m/e 246 ($\underline{M}^+$ + 1), and the isomer (23) (200 mg) (8 %); $\nu_{max.}$ ($CHCl_3$) cm^{-1}: 3410 (NH), 1750 (C = O); δ ($CDCl_3$): 0.13 (9H, s, ($C\underline{H}_3)_3Si$), 2.83 (1H, dd, J = 2 and 8 Hz, C_3-H), 3.69 (2H, t, J = 6 Hz, $C\underline{H}_2$-OH) 4.22 (1H, m, $CH_3C\underline{H}$(OH)-), 6.70 br (1H, s, $N\underline{H}$); m/e 246 ($\underline{M}^+$ + 1).

Preparation of β-Lactams (25 and 26) —— To a stirred solution of the amino ester (20) (0.353 g) and triethylamine (0.317 g) in dry benzene (10 ml) was added trimethylchlorosilane (0.778 g) at room temperature. After the stirring had been continued for 8 h at room temperature, the precipitate was filtered off and the filtrate was concentrated to give the silyl derivative (21), which was used for the next reaction without purification. To a stirred solution of 21 in dry tetrahydrofuran (10 ml) was added ethylmagnesium bromide (3 mol equivalent) at 0° in a current of nitrogen, and the resulting mixture was stirred at room temperature for 20 h. The mixture was treated with water and extracted with methylene chloride. The organic layer was washed with water and dried (Na_2SO_4). Removal of the solvent gave a yellow oil, which was dissolved in ether (40 ml) again and treated with 10 % ammonium chloride solution (10 ml) at room temperature for 20 h. The ethereal layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave a colour-

less oil, which was subjected to silica gel column chromatography. Elution with benzene-acetone (17 : 3 v/v) afforded the cis-β-lactam (26) (120.5 mg) (40.02 %); $\nu_{max.}$ ($CHCl_3$) cm^{-1}: 3425 (NH), 1750 (C = O); δ ($CDCl_3$): 1.50 (3H, d, J = 7 Hz, $CH_3CH(OH)$-), 3.23 (1H, dd, J = 5 and 10 Hz, C_3-H), 5.00 (1H, t, J = 4 Hz, $CH\langle^{O}_{O}$), 6.56 br (1H, s, NH), and the trans-β-lactam (25) (60.7 mg)(20.16 %); $\nu_{max.}$ ($CHCl_3$) cm^{-1}: 3425 (NH), 1750 (C = O); δ ($CDCl_3$): 1.33 (3H, d, J = 8 Hz, $CH_3CH(OH)$-), 2.85 (1H, dd, J= 2 and 8 Hz, C_3-H), 4.94 (1H, t, J = 3Hz, $CH\langle^{O}_{O}$), 6.58 br (1H, s, NH), Anal. calcd. for $C_{10}H_{17}NO_4$: M^+ 215.1156. Found: M^+ 215.1133.

Preparation of the Mesyloxy Derivatives (27, 29 and 30) —— To a stirred solution of the mixtures of β-lactam (23 and 24) (540 mg) in dry pyridine (5 ml) was added methanesulfonyl chloride (318 mg) at - 30°. After the stirring had been continued for 1 h at 0°, the mixture was extracted with methylene chloride. Evaporation of the solvent gave an oil, which was subjected to silica gel column chromatography. Elution with benzene-acetone (9 : 1 v/v) afforded 27 (360 mg) (50.4 %) as a colourless oil; $\nu_{max.}$ ($CHCl_3$) cm^{-1}: 3390 (NH), 1745 (C = O), 1350 (SO_2); δ ($CDCl_3$): 0.04 (9H, s, $(CH_3)_3Si$), 1.13 (3H, d, J = 6.5 Hz, $CH_3CH(OH)$-), 2.93 (3H, s, SO_2CH_3), 3.05 (1H, m, C_3-H), 3.60 (1H, m, C_4-H), 4.17 (2H, t, J = 6 Hz, CH_2OMs), 6.75 br (1H, s, NH); m/e 324 (M^+ + 1); 29 (70 mg) (7.1 %) as a colourless oil; $\nu_{max.}$ ($CHCl_3$) cm^{-1}: 3390 (NH), 1745 (C= O), 1350 (SO_2); δ ($CDCl_3$): 1.29 (3H, d, J = 6.5 Hz, $CH_3CH(OH)$-), 2.79 (1H, m, C_3-H), 3.00 (3H, s, SO_2CH_3), 3.67 (1H, m, C_4-H), 4.23 (2H, t, J = 6Hz, CH_2-OMs), 6.43 br (1H, s, NH), and 30 (100 mg) (16.7 %) as a colourless oil; $\nu_{max.}$ ($CHCl_3$) cm^{-1}: 3390 (NH), 1745 (C = O), 1350 (SO_2); δ ($CDCl_3$): 1.41 (3H, d, J = 6.5 Hz, $CH_3CH(OH)$-), 3.03 (3H, s, SO_2CH_3), 3.18 (1H, m, C_3-H), 3.73 (1H, m, C_4-H), 4.25 (2H, t, J = 6 Hz, CH_2-OMs), 6.43 br (1H, s, NH).

Formation of the Carbanenam Derivative (28) —— To a stirred solution of the mesylate (27) (100 mg) in dry tetrahydrofuran (10 ml) was added lithium hexamethyl disilazide (1 mol equivalent) in tetrahydrofuran at - 30° in a current of nitrogen. The mixture was then warmed up to 10° over the period of 2 h, and further stirred for 2 h at 10°. The mixture was treated with water, and extracted with methylene chloride. The organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave a colourless oil, which was chromatographed on silica gel using benzene-acetone (95 : 5 v/v) as eluant to afford the bicyclic compound (28) (52 mg) (73.9 %); $\nu_{max.}$ ($CHCl_3$) cm^{-1} : 1740 (C = O); δ ($CDCl_3$): 0.15 (9H, s, $(CH_3)_3Si$), 1.32 (3H, d, J = 6.5 Hz, $CH_3CH(OH)$-), 3.28 (1H, dd, J = 5.3 and 9.3 Hz, C_6-H), 4.02 (1H, dt, J = 6.5 and 9.3 Hz, C_8-H); Anal. Calcd. for $C_{11}H_{21}NO_2Si$: M^+ 227.1342. Found: M^+ 227.1354.

Table 1

Spectral Data / Compound	IR $\nu_{max}^{CHCl_3}$ cm^{-1}	NMR (δ)	Mass	Elemental analysis	Yield (%)
(10)	1720(C = O)	1.45(3H, d, J = 6 Hz, C_5-CH_3) 2.10(3H, s, -OAc) 2.83(2H, t, J = 7 Hz, CH_2-C=N) 3.78(1H, d, J = 12 Hz, C_4-H) 3.86(3H, s, -OCH_3) 4.43(2H, t, J = 7 Hz, CH_2-OAc) 4.97(1H, dq, J = 6 and 12 Hz, C_5-H)	230 (M^+ + 1)	Anal. calcd. C, 52.39; H, 6.60; N, 6.11 Found. C, 52.68; H, 6.82; N, 5.92	30.78
(11)	1720(C = O)	1.33 (3H, d, J = 6 Hz, C_4-CH_3) 3.55(1H, m, C_4-H) 4.62(1H, d, J = 12 Hz, C_5-H)	230 (M^+ + 1)		18.28
(12)	1720(C = O)	1.45(3H, d, J = 6 Hz, C_5-CH_3) 2.03(3H, s, OAc) 3.58(1H, d, J = 9 Hz, C_4-H) 3.80(3H, s, -OCH_3) 4.15(2H, t, J = 7 Hz, CH_2-OAc) 4.83(1H, m, C_5-H)	244 (M^+ + 1)	Anal. calcd. C, 54.31; H, 7.04; N, 5.76 Found. C, 54.17; H, 7.07; N, 5.50	37.5
(13)	1720(C = O)	1.30(3H, d, J = 6 Hz, C_4-CH_3) 2.00(3H, s, OAc) 3.45(1H, m, C_4-H) 3.78(3H, s, OCH_3) 4.15(2H, t, J = 7 Hz, CH_2-OAc) 4.45(1H, d, J = 7 Hz, C_5-H)	244 (M^+ + 1)		20.5
(14)	1730(C = O)	1.35(3H, d, J = 7 Hz, C_5-CH_3) 3.76(3H, s, OCH_3) 3.88(4H, br, OCH_2CH_2O) 4.92(1H, t, $CH<^{O}_{O}$)		Anal. calcd. C, 54.31; H, 7.16; N, 5.76 Found. C, 53.93; H, 7.16; N, 5.56	45.6
(15)	1730(C = O)	1.30(3H, d, J = 7 Hz, C_4-CH_3) 3.73(3H, s, OCH_3) 3.86(4H, br, -OCH_2CH_2O) 4.38(1H, d, J = 7 Hz, C_5-H) 4.92(1H, t, J = 4 Hz, $CH<^{O}_{O}$)			20.0

Table 2

Spectral Data / Compound	IR $\nu_{max}^{CHCl_3}$ cm^{-1}	NMR (δ)	Mass	Elemental analysis	Yield (%)
(18)	1720(C = O)	1.07(3H, d, J = 7 Hz, $CH_3CH(OH)$) 2.02(3H, s, OAc) 3.68(3H, s, OCH_3) 4.08(2H, t, J = 6 Hz, CH_2OAc)	248 (M^+ + 1)	Anal. calcd. C, 53.42; H, 8.56; N, 5.36 Found. C, 53.28; H, 8.65; N, 5.36	98
cis (20)	1725(C = O)	1.24(3H, d, J = 8 Hz, $CH_3CH(OH)$) 3.75(3H, s, OCH_3) 3.91(4H, br, OCH_2CH_2O) 4.71(1H, t, J = 4 Hz, $CH<^{O}_{O}$)	248 (M^+ + 1)		10.2
trans (20)	1725(C = O)	1.16(3H, d, J = 8 Hz, $CH_3CH(OH)$)			23.8
(22)	1735(C = O) 1710(C = O)	1.20(3H, d, J = 6 Hz, $CH_3CH(OH)$) 3.47(1H, dd, J = 4 and 10 Hz, $CH(CO_2Me)$) 3.73, 3.83(6H, each s, 2 x OCH_3) 4.24(1H, dq, J = 4 and 6 Hz, $CH(OH)$)	260 (M^+ + 1)	Anal. calcd. C, 50.96; H, 6.61; N, 5.40 Found. C, 50.67; H, 6.77; N, 4.96	88

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