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TOWARD THE ASSIGNMENT OF LIPOSIDOMYCIN STEREOCHEMISTRY: SYNTHESIS OF 1,4-DIAZEPAN-3-ONE ANALOGUES BY REDUCTIVE AMINATION APPROACH ‡

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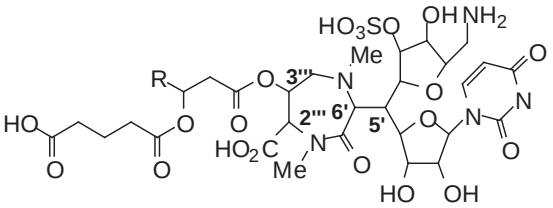
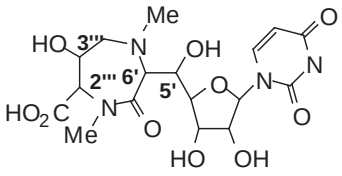
Abstract- Toward the assignment of liposidomycin stereochemistry, a stereocontrolled synthesis of the liposidomycin diazepanone ring system and two precursors, has been achieved. The NMR coupling constants of a 5-phenyl model compound closely related to the liposidomycin diazepanone degradation product.

Liposidomycins, found in the culture filtrate and mycelia of *Streptomyces griseosporeus* by Isono and co-workers in 1985 as a family of novel lipid-containing nucleoside antibiotics, strongly inhibit bacterial peptidoglycan synthesis.[1,2] The primary site of action of liposidomycin was determined to be at phospho-*N*-acetylmuramylpentapeptide transferase (Translocase I), the first step in the lipid cycle of peptidoglycan synthesis in the cell wall of *E. coli* at 0.03 μg/mL, which is three orders of magnitude greater activity than that of tunicamycins and is extremely specific.[2] The structures of liposidomycins, A, B and C, were ascribed to **1a**, **1b** and **1c**, respectively, based on degradation studies and spectroscopic evidence.[3] Because of the flexibility of the seven-membered ring and the unusual nature of the ring atoms and substituent, the relative and absolute stereochemistry at three carbons on the





1a: LiposidomycinA : R = $Me(CH_2)_4$–CH=CH–$(CH_2)_3$ **2**: Liposidomycin degradation product
1b: LiposidomycinB : R = $Me_2CH(CH_2)_8$
1c: LiposidomycinC: R = $Me(CH_2)_{10}$

Figure 1

‡ This Paper is dedicated to the celebration of the 75th birthday of Professor Yuichi Kanaoka.

diazepanone ring (2’’’, 3’’’ and 6’) and one in the junction between diazepanone and nucleoside moieties (5’) has not been established. With the limited supply of material for further degradation or crystallographic studies, the synthesis of model compounds and degradation product (**2**) becomes an important tool for structural assignment. Several research groups have engaged in the respective synthesis of a ribosyl-substituted diazepanone,[4] a diazepanone nucleoside,[5] a nucleoside disaccharide,[6] and an isoascorbic acid derived diazepanone.[7] Particularly, Knapp and co-workers recently reported the synthesis of 1,4-diazepan-3-one compounds[8] and the assignment of liposidomycin diazepanone stereochemistry as 6’(*S*), 2’’’(*S*) and 3’’’(*S*) or its enantiomer.[9] We report here the synthesis of **4** and **6**, which are possible synthetic precursors of liposidomycin 1,4-diazepan-3-ones (**3** and **5**). Through the synthesis of these compounds, the construction and functional group introduction on the 1,4-diazepan-3-one ring system are demonstrated.

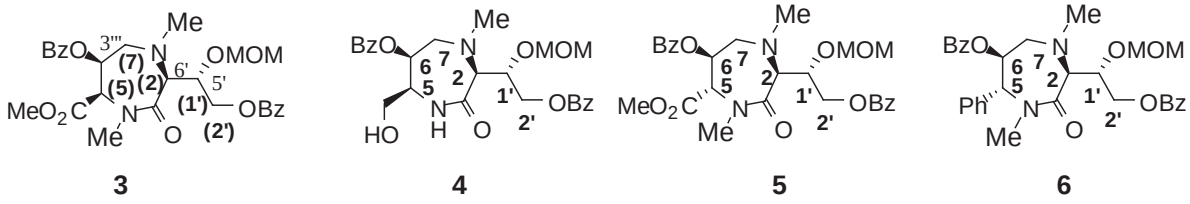
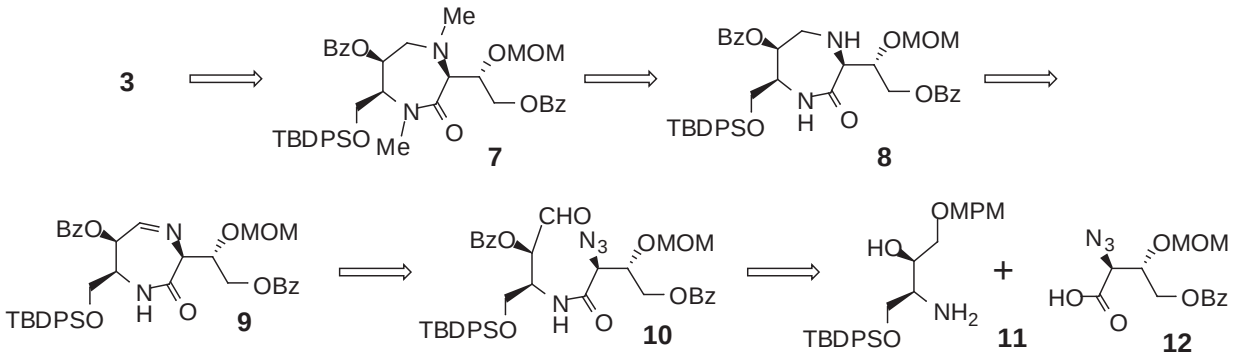


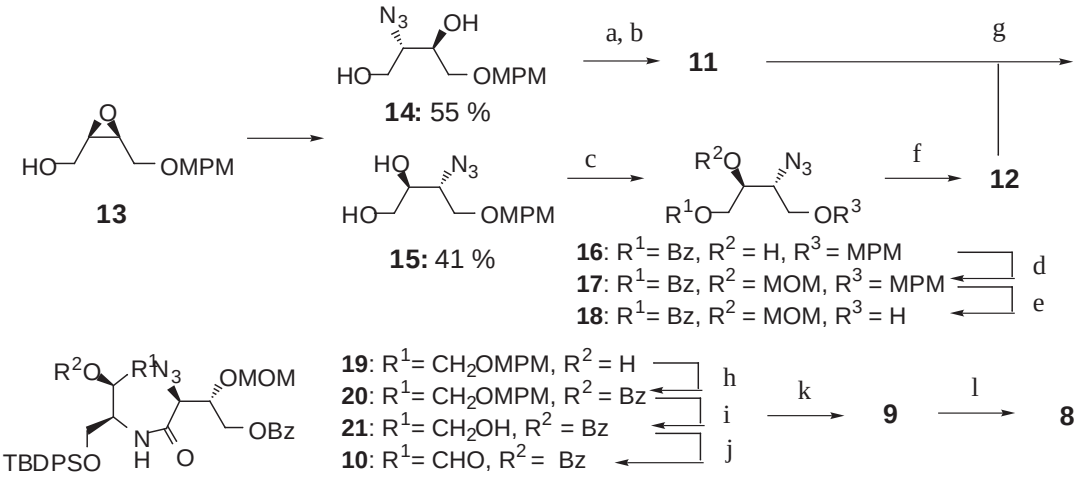
Figure 2

Our retrosynthetic plane of diazepanone compound (**3**) was outlined in Scheme 1. As carboxylic acid will be constructed at the final synthetic stage, benzoyl (Bz), methoxymethyl (MOM) and *tert*-butyldiphenylsilyl (TBDPS) protection groups were chosen for the C-2’ and C-1’ hydroxy and C-5 hydroxymethyl groups. Introduction of two *N*-methyl groups on the diazepanone ring was planned after diazepanone ring closure. The 1,4-diazepan-3-one ring system (**8**) was constructed *via* intramolecular imine formation (**9**) from a dipeptide fragment (**10**), which contained an aldehyde and an amine moiety. The dipeptide fragment was prepared by coupling between the amino alcohol fragment (**11**) and α-azido acid (**12**).



Scheme 1

Starting from 2-azido-1,3-diol (**14**) and 3-azido-1,2-diol (**15**) obtained from known 4-methoxybenzyl (MPM) protected 2,3-epoxy alcohol (**13**)[10] by sodium azide (NaN_3) treatment,[4] the 1,3-diol (**14**) was converted into **11** by TBDPS protection and following azide reduction by 10 %Pd-C/H_2 in 80% yield. On the other hand, the 1,2-diol (**15**) was converted into carboxylic acid (**12**) in a 4 step-sequence; Bz and MOM protection, the deprotection of the MPM group with DDQ and PDC oxidation in DMF. Coupling of two fragments (**11**) and (**12**) was achieved with DCC and HOAt in THF to give **19** in 62% yield. Bz protection of the secondary alcohol and DDQ deprotection of the MPM group gave **21**, which was subjected to Swern oxidation to give aldehyde (**10**) in 96% yield. On treatment of **10** with 10% Pd-C under H_2 atmosphere in the presence of AcOH, imine (**9**) was isolated in 59% yield. Hydrogenation of imine with $NaBH_3CN$ afforded 1,4-diazepan-3-one derivative (**8**) in 91% yield.

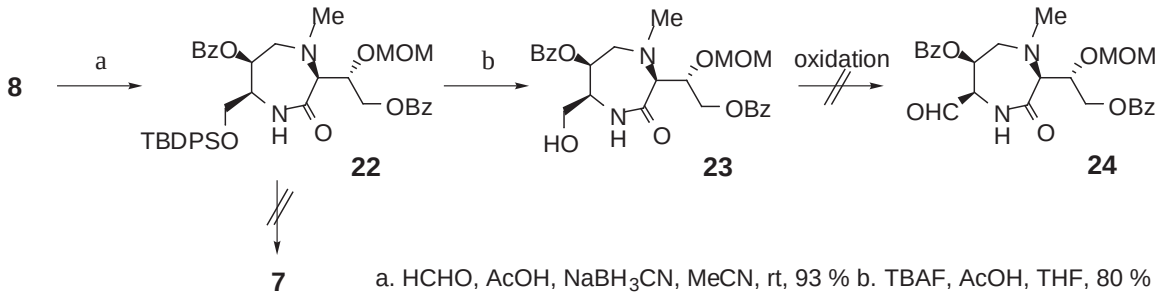


a. TBDPSCl, imidazole, CH_2Cl_2, rt, 85 % b. 10 % Pd-C/ H_2, EtOAc, 80 % c. BzCl, Et_3N, DMAP, CH_2Cl_2, 0˚C, 76% d. MOMCl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, 40˚C, 88% e. DDQ, CH_2Cl_2 / H_2O, rt, quant. f. PDC, DMF, rt g. DCC, HOAt, THF, rt, 62 % (2 steps) h. BzCl, TEA, DMAP, CH_2Cl_2, 100 % i. DDQ, CH_2Cl_2 / H_2O, rt, 89 % j. DMSO / $(COCl)_2$, Et_3N, CH_2Cl_2, 96 % k. 10 % Pd-C/ H_2, AcOH, EtOAc, rt, 59 % l. $NaBH_3CN$, AcOH, MeOH, rt. 91 %

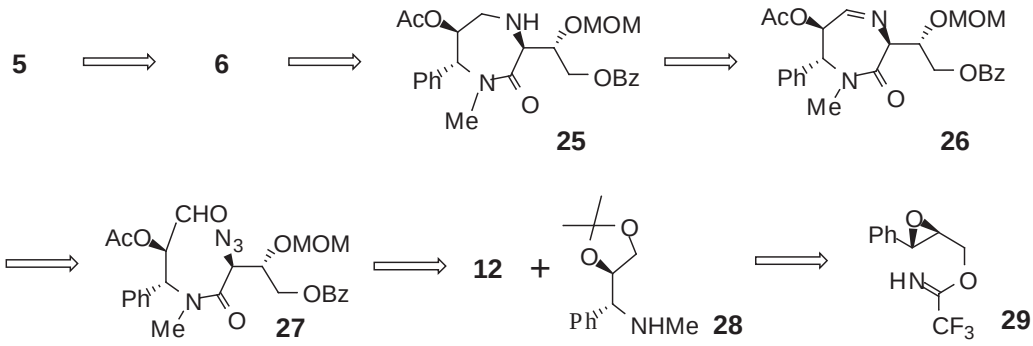
Scheme 2

Methylation at the *N*-1 and *N*-4 positions was examined. On treatment of **8** with HCHO, AcOH and $NaBH_3CN$ in MeCN, the *N*-1 position was methylated to give **22** in 93% yield. Further methylation at the *N*-4 position failed under various conditions. The TBDPS group of **22** was removed with TBAF in the presence of AcOH in THF to yield alcohol (**23**) in 80% yield.[11] Oxidation of primary hydroxy group with such as PDC, Dess-Martin periodinane, and tetra-n-propylammonium perruthenate, was unsuccessful.

Based on the above results, in the synthesis of **5**, a carboxylic acid equivalent (Ph) and the *N*-4 methyl group were introduced before the 1,4-diazepan-3-one ring construction. The 1,4-diazepan-3-one ring system was also constructed *via* imine (**26**) from the dipeptide fragment (**27**), which was prepared from the coupling of **12** and *N*-methylamine**.** The starting amine fragment (**28**) was obtained from phenylglycidyl trifluoroacetimidate (**29**).



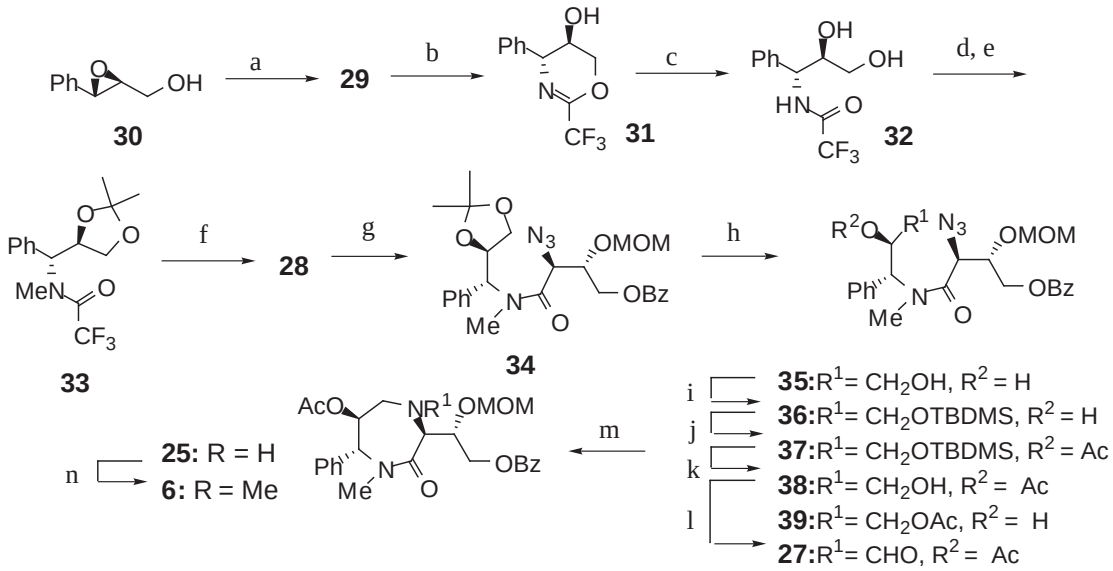
Scheme 3



Scheme 4

Trifluoroacetonitrile and (2*S*,3*S*)-3-phenylglycidol (**30**) was condensed under our reported method[13] to yield **29** in 87% yield. On treatment of **29** with 0.5 eq. of Et_2AlCl in CH_2Cl_2 at 0˚C, cyclization took place selectively at the benzylic position to give 94% yield of dihydrooxazolines (**31**), which was hydrolyzed to 1,2-diol (**32**) in 80% yield.[14] Protection of the 1,2-diol as an acetonide and methylation of trifluoroacetamide afforded **33**. The trifluoroacetamide group of **33** was easily removable under alkaline conditions (K_2CO_3, MeOH, H_2O 100°C) to afford **28** in 93% yield. Although epoxy trichloroacetamide is known as a useful intermediate for synthetic organic chemistry,[15] unfortunately, cleavage of the corresponding trichloroacetamide group of **33** did not proceed and no amount of **28** was obtained. Coupling of acid chloride of **12** with **28** in CH_2Cl_2 afforded **34** in 61% yield.[16] Acid hydrolysis of the acetonide group readily gave 1,2-diol (**35**) in 85% yield. Sequential protection of the primary hydroxy group with the TBDMS group and the secondary hydroxy group with the Ac group afforded **37** in 93% yield. Careful acid treatment of **37** gave primary alcohol (**38**) and the following Swern oxidation gave aldehyde (**27**) in 86% yield. TBDMS deprotection by TBAF and/or strong acidic conditions caused Ac migration to give secondary alcohol (**39**). Diazepanone ring closure was achieved by 10% Pd-C under H_2 atmosphere conditions and 1,4-diazepan-3-one (**25**) was directly obtained from **27** in 94% yield. Finally, *N*-1 methylation of **25** by HCHO, AcOH and $NaBH_3CN$ in MeCN afforded **6**[17] in 87% yield.

^1H and ^{13}C NMR spectral data reported for the liposidomycin degradation product (**2**) and synthetic compounds (**4**) and (**6**) are shown in Table 1. The signals for **6** match closely those of **2**. In particular, the respective signals of H-6 for **4** are dt, J = 9.5, 2.2 Hz and for **6** are dt, J = 4.6, 2.2Hz, compared



a. trifluoroacetamide, $(COCl)_2$ (3.0 eq.), DMSO (15 eq.), Et_3N (10 eq.), CH_2Cl_2, -78 °C and then DBU, **30**, 87 % b. Et_2AlCl (0.5 eq.), CH_2Cl_2, rt, 94 % c. BF_3•Et_2O (0.5 eq.), CH_2Cl_2, -25°C and then H_20, 80 % d. 2,2-dimethoxypropane, CSA, CH_2Cl_2, rt e. NaH, MeI, THF, DMSO, 0°C, 80 % (2 steps) f. K_2CO_3, MeOH, H_2O, 100°C, 93 %. g. **12**, $(COCl)_2$, then **28**, $(Me_2CH)_2NEt$, THF, rt, 61 % h. 1N HCl-THF, 50°C, 82 % i. TBSCl, imidazole, CH_2Cl_2, 83 % j. Ac_2O, TEA, DMAP, CH_2Cl_2, 99 % k. 1N HCl-THF, 50 °C, 98 % l. DMSO / $(COCl)_2$, Et_3N, CH_2Cl_2, 99 % m. 10 % Pd-C/ H_2, AcOH, EtOAc, rt, 90 % n. HCHO, AcOH, $NaBH_3CN$, MeCN, rt, 87 %.

Scheme 5

with dt, *J* = 4.8, 2.7 Hz for H-3''' of **2**. Also, the respective signals of H-7 for **4** are dd, *J* = 2.2, 13.4 Hz, dd, *J* = 9.5, 13.4 Hz and for **6** are a couple of dd, *J* = 2.2, 15.6 Hz, compared with a couple of dd, *J* = 2.7, 15.3 Hz for H-4''' of **2**.

Table 1. ^{1}H-NMR spectral data of 1,4-diazepan-3-one compounds

position	**2** (in D_2O)	**4** (in $CDCl_3$)	**6** (in $CDCl_3$)
6' (2)	3.68, d, *J* = 10 Hz	3.45, d, *J* = 3.1 Hz	3.43, d, *J* = 9.2 Hz
2''' (5)	4.22, d, *J* = 4.8 Hz	4.60, dddd, *J* = 2.2, 5.0, 8.1, 9.8 Hz	4.90, d, *J* = 4.6 Hz
3''' (6)	4.46, dt, *J* =4.8, 2.7 Hz	5.72, dt, *J* = 9.5, 2.2 Hz	5.70, dt, *J* = 4.6, 2.2 Hz
4''' (7)	3.16, br dd, *J* = 2.7, 15.3 Hz	2.70, dd, *J* = 2.2, 13.4 Hz	3.27, dd, *J* = 2.2, 15.6 Hz
4''' (7)	3.21, dd, *J* = 2.7, 15.3 Hz	3.29, dd, *J* = 9.5, 13.4 Hz	3.42, dd, *J* = 2.2, 15.6 Hz

In conclusion, two liposidomycin diazepanone derivatives (**4** and **6**), precursors of penta-substituted 5(*R*) and 5(*S*) liposidomycin diazepanone derivatives (**3** and **5**), have been synthesized. The reductive amination approach to diazepanone ring is rather simple and easy to perform in high yield. Although conformational analysis of the presented compounds by molecular modeling (MM) calculations is still required, the stereochemistry for the liposidomycin degradation product (**2**) is suggested to be 5'(*S*), 6'(*S*), 2'''(*S*) and 3'''(*S*) or its enantiomer. The synthesis of 2'''*R*- and 2'''*S*-liposidomycin diazepanone (**3** and **5**) and their conformational analyses by MM calculations are an on-going project, and will be reported in due course.

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8. The numbering system for the seven-membered heterocycle in structure (**1**) correlates with that of perhydro-1,4-diazepins in which C-2''' corresponds to C-5, C-3''' to C-6, and C-4''' to C-7.
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11. On the treatment of C6-Ac compound with TBAF and AcOH, Ac migration was occurred to C5-hydroxymethyl position in 93% yield.
12. Data for **4**: Rf 0.1 (CH_2Cl_2/MeOH, 20/1); $[\alpha]_D^{29.1}$ = 22.1° (c = 0.3, $CHCl_3$); ^{1}H-NMR(400 MHz, $CDCl_3$) 8.14-8.11 (2H, m, HC(Ar)), 7.90-7.88 (2H, m, HC(Ar)), 7.63 (1H, d, *J* = 9.8 Hz, NH), 7.57-7.49 (2H, m, HC(Ar)), 7.43-7.36 (4H, m, HC(Ar)), 5.72 (1H, dt, *J* = 9.5, 2.2 Hz, HC(6)), 4.92 (1H, d, *J* = 5.4 Hz), 4.66 (1H, d, *J* = 5.4 Hz), 4.60 (1H, dddd, *J* = 2.2, 5.0, 8.1, 9.8 Hz, HC(5)), 4.32 (2H, d, *J* = 5.8 Hz, HC(2')), 4.22 (1H, dt, *J* = 3.1, 5.8 Hz, HC(1')), 3.63 (1H, dd, *J* = 5.0, 11.5 Hz, HC(8)), 3.55 (1H, dd, *J* = 8.1, 11.5 Hz, HC(8)), 3.45 (1H, d, *J* = 3.1 Hz, HC(2)), 3.29 (1H, dd, *J* = 9.5, 13.4 Hz, HC(7)), 3.19 (3H, s, H_3C), 2.95 (1H, brs, OH), 2.70 (1H, dd, *J* = 2.2, 13.4 Hz, HC(7)), 2.68 (3H, s, H_3C); ^{13}C-NMR (100 MHz, $CDCl_3$) 169.3, 167.3, 166.1, 133.5, 133.3, 130.9, 130.1, 129.6, 129.4, 128.5, 128.2, 96.3, 74.9, 70.4, 68.4, 63.1, 61.8, 57.5, 56.1, 51.9, 44.0; IR (neat, cm^{-1}); 3360 (m), 2930 (m), 1721 (s), 1659 (m), 1273 (s), 1111 (s), 1070 (s), 1026 (m), 712 (m); FAB-MS 499 ($[M+Na]^+$, 26), 488 (36), 487 (MH^+, 100); FAB-HRMS calcd for $C_{25}H_{31}N_2O_8$ (MH^+); 487.2080; found 487.2068.

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16. Coupling of **26** and **11** with DCC/HOAt in THF afforded a 1:1.5 mixture of **32** and its benzylic isomer in 57% yield.
17. Data for **6**: Rf 0.28 (hexane/EtOAc, 1/1); $[\alpha]_D^{23.8}$ = 31.7° (c = 0.43, $CHCl_3$); ^{1}H-NMR（400 MHz, $CDCl_3$) 7.76 (2H, d, *J* = 8.1 Hz, HC(Ar)), 7.54 (1H, t, *J* = 8.1 Hz, HC(Ar)), 7.36 (2H, t, *J* = 8.1 Hz, HC(Ar)), 7.20-7.18 (4H, m, HC(Ar)), 7.07-6.98 (1H, m, HC(Ar)), 6.13 (1H, d, *J* = 8.6 Hz, HC(1')), 5.70 (1H, dt, *J* = 4.7, 2.2 Hz, HC(6)), 4.90 (1H, d, *J* = 4.7 Hz, HC(5)), 4.76 (1H, d, *J* = 6.8 Hz, HC), 4.70 (1H, d, *J* = 6.8 Hz, HC), 4.58 (1H, dd, *J* = 3.4, 11.7 Hz, HC(2')), 4.39 (1H, ddd, *J* = 3.4, 4.1, 9.3 Hz, HC(1')), 4.25 (1H, dd, *J* = 4.1, 11.7 Hz, HC(2')), 3.43 (1H, d, *J* = 9.3 Hz, HC(2)), 3.42 (1H, dd, *J* = 2.2, 15.6 Hz, HC(7)), 3.31 (3H, s, H_3C), 3.27 (1H, dd, *J* = 2.2, 15.6 Hz, HC(7)), 3.24 (3H, s, H_3C), 2.52 (3H, s, H_3C), 2.16 (3H, s, H_3C); ^{13}C-NMR (100 MHz, $CDCl_3$) 172.4, 170.2, 166.4, 136.2, 132.8, 130.1, 129.7, 129.4, 128.2, 127.9, 124.8, 96.4, 72.8, 72.2, 65.2, 65.0, 64.1, 56.1, 55.7, 38.6, 37.2, 21.2; IR (neat, cm^{-1}); 2936 (m), 1738 (s), 1721 (s), 1646 (s), 1451 (m), 1374 (m), 1275 (s), 1237 (s), 1034 (s), 918 (m), 733 (m), 714 (s), 700 (m); FAB-MS 486 (18.3), 485 (MH^+, 87), 453 (47), 413 (100), 391 (94); FAB-HRMS calcd for $C_{26}H_{33}N_2O_7$ (MH^+); 485.2288; found 485.2277.