SYNTHESIS AND ACTIVITY OF C-21 ALKYLAMINO DERIVATIVES OF (9*R*)-ERYTHROMYCYLAMINE

PAUL A. LARTEY, SHARI L. DENINNO, RAMIN FAGHIH, DWIGHT J. HARDY, JACOB J. CLEMENT and JACOB J. PLATTNER

Anti-Infective Drug Discovery, Abbott Laboratories, Abbott Park, IL 60064, U.S.A.

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Novel analogs of (9*R*)-9-deoxo-9-(*N*,*N*-dimethylamino)erythromycin A bearing *N*-alkylamino substituents at the C-21 position were synthesized. These compounds retained antibacterial activity. The C-21 *N*,*N*-dimethylamino analog showed a modest improvement in activity against some Gram-negative bacteria.

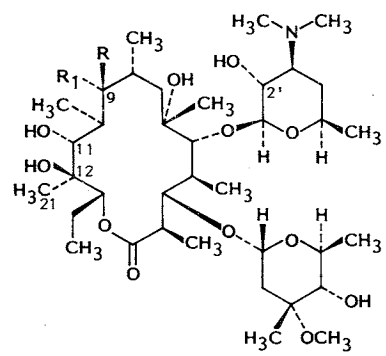
A number of novel synthetic modifications of erythromycin A (**1**) have been reported, some of which have led to clinically useful compounds with improved pharmacokinetics[1] and expanded antibacterial spectrum[2] compared to **1**. Of particular interest to us are compounds containing basic amino groups in the macrolactone. As previously reported[3], (9*R*)-9-alkylamino derivatives of **1**, such as compound **2**, retain the antibacterial spectrum of **1** and in addition afford significant improvements in pharmacokinetics[4]. We considered it of interest to introduce a second basic amine into the macrolactone ring of **2** and to study the effects of such modifications on the spectrum of antibacterial activity.

The C-21 position, normally a methyl group, was selected for transformation into an alkylamino moiety, thereby converting a lipophilic region of the molecule into a polar and positively charged one. In this communication, we report the syntheses of novel analogs of **2** bearing *N*-benzyl-*N*-methylamino, *N*-methylamino and *N*,*N*-dimethylamino groups at C-21. The *in vitro* antibacterial activities of these compounds are also discussed.

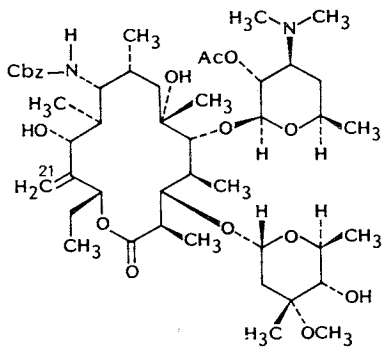
Chemistry

We recently described a selective protection of (9*R*)-erythromycylamine which allowed access to the C-12, 21-olefin intermediate **3**. Epoxidation of this olefin was highly stereoselective as the reaction was directed by the C-11 hydroxyl group[5]. Subsequent selective deprotection of the resulting epoxide led to the key intermediate **4**. As shown in Scheme 1, compound **4** underwent a facile and regioselective epoxide opening, upon treatment with benzylamine and in the presence of neutral alumina, to afford the versatile C-21 *N*-benzylamino intermediate **5**.

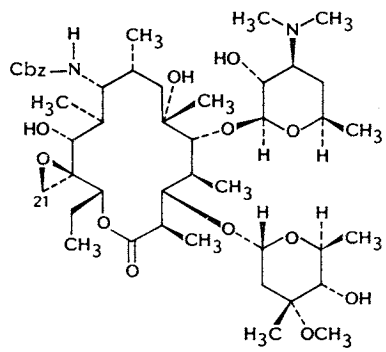
Brief hydrogenolysis of **5** (1 hour) over Pd-C and in EtOAc selectively afforded the 9-*N*-deprotected compound **6**. However, both the yield of **6** and its ratio to the fully deprotected intermediate **7** could not be reproduced consistently.



1 R=R$_1$=O
2 R=H R$_1$=N(CH$_3$)$_2$



3



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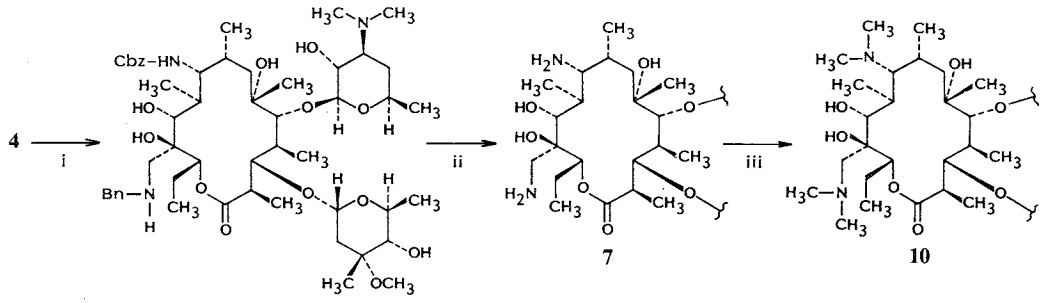
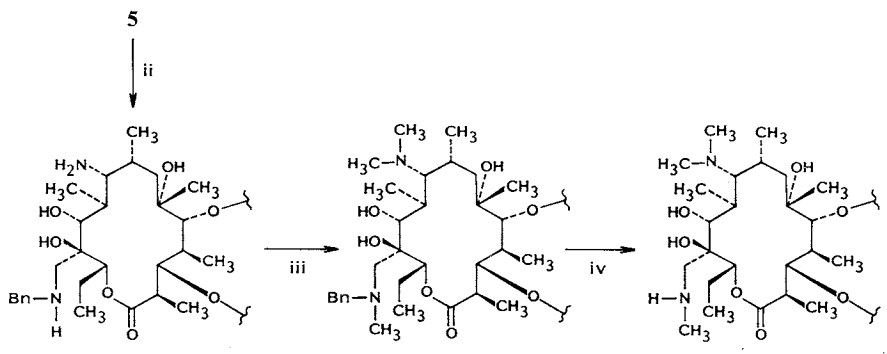
Scheme 1.





i: $BnNH_2$, Al_2O_3, $CH_3OC_2H_4OH$, ii: H_2, Pd-C, CH_3OH, iii: HCHO, $NaBH_3CN$, CH_3COOH, iv: H_2, $Pd(OH)_2$.

Therefore, for the purposes described herein, we settled for conditions that led to a 1 : 1 mixture of **6** and **7**, both of which were useful in the syntheses of the desired compounds.

Thus, reductive alkylation of **6** with formaldehyde led to the C-21 *N*-benzyl-*N*-methyl amino analog **8**. Subsequent hydrogenolysis of **8** afforded the C-21 *N*-methylamino analog **9**. Reductive alkylation of **7** under similar conditions led to the C-21 *N*,*N*-dimethylamino congener **10**. Hence, compound **5** served as a central intermediate for all the compounds described in this communication.

Biological Results

The minimum inhibitory concentrations (MIC) of each compound was determined against laboratory

Table 1. Antibacterial activities of C-21 alkylamino derivatives of (9*R*)-9-deoxo-9-(*N*,*N*-dimethylamino)erythromycin A.

Strain No.		Minimum inhibitory concentration (μg/ml)			
		2	**8**	**9**	**10**
Streptococcus pyogenes	EES6	0.05	0.78	0.78	0.10
S. bovis	A5169	0.1	0.10	0.78	0.05
S. agalactiae	CMX 508	0.1	0.39	1.56	0.10
S. pyogenes	930 CONST	>100	50	>100	>100
S. pyogenes	2548 INDUC	100	12.5	50	25
Staphylococcus aureus	ATCC 6538P	0.39	12.5	12.5	1.56
S. aureus	45	0.78	6.2	6.2	1.56
S. epidermidis	3519	0.39	6.2	12.5	3.1
Micrococcus luteus	ATCC 9341	0.1	0.39	1.56	0.2
M. luteus	ATCC 4698	0.1	3.1	1.56	0.78
Enterococcus faecium	ATCC 8043	0.2	1.56	3.1	0.39
Escherichia coli	JUHL	>100	100	50	12.5
E. coli	SS	0.39	1.56	0.78	0.2
E. coli	DC-2	50	100	50	6.2
E. coli	H560	25	50	12.5	3.1
E. coli	KNK 437	100	100	25	12.5
Enterobacter aerogenes	ATCC 13048	100	>100	100	25
Klebsiella pneumoniae	ATCC 8045	50	100	50	6.2
Pseudomonas aeruginosa	K799/61	>100	12.5	3.1	1.56
Haemophilus influenzae	504	16	32	32	8
H. influenzae	519A	8	8	32	4
H. influenzae	1177	2	2	4	0.5

bacterial strains by standard[6] agar dilution methods. As shown in Table 1, all three compounds retained antibacterial activity. Compound **10** was equal to **2** in potency against most of the susceptible Gram-positive bacteria, while **8** and **9** were significantly less potent. None of the three compounds showed significant improvement in potency against the resistant (MLS)[7] Gram-positive organisms, *Streptococcus pyogenes* 930 CONST and 2548 INDUC. The C-21 *N*,*N*-dimethylamino analog **10** showed notable improvements in activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Haemophilus influenzae*.

Conclusion

Introduction of an alkylamino substituent at the otherwise lipophilic C-21 position of (9*R*)-9-(*N*,*N*-dimethylamino)erythromycin A, provides compounds in which antibacterial activity has been retained. Albeit significant, the change in antibacterial spectrum observed for the C-21 *N*,*N*-dimethylamino analog **10** is considered to be modest. Several other C-21 alkylamino derivatives need to be investigated before any firm structure-activity correlations can be deduced. The potential utility of the compounds described in this communication will depend on other factors such as pharmacokinetics and potency in *in vivo* models.

Experimental

All ^{1}H and ^{13}C NMR spectra were recorded on a GE-Nicolet QE-300 at 300 MHz, except the ^{1}H NMR spectrum of **5**, which was recorded at 500 MHz on a General Electric GN-500. Chemical shifts are reported as ppm from TMS as internal standard. Mass spectra were recorded on a Kratos MS 50 spectrometer and optical rotations determined with a Perkin-Elmer 241 polarimeter. EM Science silica

gel 60 (230~400 mesh) was used in the purification of all compounds. Synthesis of **4** has been previously reported from our laboratory.

(9*R*)-21-(*N*-Benzylamino)-9-(*N*-carbobenzyloxyamino)-9-deoxoerythromycin A (**5**)

Neutral alumina (922 mg) was added to a stirring solution of **4** (256 mg, 0.295 mmol) in 5 ml methoxyethanol at room temperature. Benzylamine (324 μl, 2.96 mmol) was added and the solution was heated to reflux. After stirring overnight, the solution was cooled to room temperature and diluted with 5% NaH_2PO_4 solution (20 ml). The layers were separated and the aqueous layer was extracted with methylene chloride (3 × 20 ml). The combined organic extracts was washed with brine (1 × 25 ml), dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The residue was chromatographed over silica gel (5% MeOH, 0.5% NH_4OH in CH_2Cl_2) to yield 198.5 mg (70%) of **5** as a white solid: $[\alpha]_D^{25}$ −36.8° (*c* 2.3, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6) δ 0.80 (3H, t, J=6.5 Hz), 0.87 (3H, d, J=7.0 Hz), 0.99 (3H, d, J=6.0 Hz), 1.0 (3H, d, J=6.0 Hz), 1.10 (6H, d, J=6.0 Hz), 1.1 (6H, s), 1.19 (3H, s), 1.20 (3H, d, J=6.0 Hz), 1.49~1.65 (5H, m), 1.75~1.90 (3H, m), 2.15 (1H, m), 2.25 (6H, s), 2.3 (1H, d, J=12.0 Hz), 2.5 (1H, m), 2.55 (1H, d, J=12 Hz), 2.7 (1H, d, J=12 Hz), 2.71 (1H, m), 2.95 (1H, dd, J=7.5 and 10 Hz), 3.13 (1H, dd, J=6.0 and 10 Hz), 4.0~4.1 (2H, m), 4.5 (1H, d, J=7.0 Hz), 4.82 (1H, d, J=5.0 Hz), 5.0 (2H, d, J=12.5 Hz), 5.09 (2H, d, J=12.5 Hz), 7.19~7.4 (10H, m); ^{13}C NMR (DMSO) δ 9.09, 10.91, 10.96, 18.35, 20.86, 21.08, 33.60, 34.50, 38.90, 40.15, 48.53, 50.90, 53.68, 64.74, 67.15, 70.08, 72.42, 74.0, 75.52, 76.80, 77.41, 78.98, 126.37, 127.19, 127.37, 127.55, 127.92, 128.07, 137.37, 140.26, 156.72; IR ($CDCl_3$) cm^{-1} 2968, 2940, 1720, 1600, 1510, 1450, 1380, 1280, 1220, 1160, 1105, 1095, 1050, 1000; MS *m/z* 974 $(M+H)^+$.

Anal Calcd for $C_{52}H_{83}N_3O_{14}$: C 64.11, H 8.59, N 4.31.
Found: C 63.77, H 8.81, N 4.23.

(9*R*)-9-Amino-21-(*N*-benzylamino)-9-deoxoerythromycin A (**6**) and (9*R*)-9-Deoxo-9,21-diaminoerythromycin A (**7**)

Palladium on carbon catalyst (10%) was added to a stirring solution of **5** (128 mg, 0.132 mmol) in 3 ml MeOH under a nitrogen atmosphere at room temperature. The solution was hydrogenated for 4 hours and the reaction monitored to completion by TLC. The catalyst was filtered off under nitrogen and washed repeatedly with excess MeOH and CH_2Cl_2. The combined filtrate and washings was concentrated, the residue redissolved in water, adjusted to pH 9 with NH_4OH and extracted with ethyl acetate (3 × 20 ml) and methylene chloride (15 ml). The combined extracts was washed with brine (20 ml), dried ($MgSO_4$) and concentrated. The residue was chromatographed over silica gel (10% MeOH, 1% NH_4OH in CH_2Cl_2 followed by 20% MeOH, 2% NH_4OH in CH_2Cl_2) to yield 34.5 mg (31%) of **6** as a white solid: $[\alpha]_D^{25}$ −40.43° (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.86 (3H, t, J=6.0 Hz), 1.0 (3H, d, J=6.3 Hz), 1.10 (6H, d, J=6.3 Hz), 1.20 (3H, d, J=6.3 Hz), 1.24 (3H, d, J=6.0 Hz), 1.25 (3H, s), 1.26 (1H, m), 1.30 (3H, s), 1.31 (3H, d, J=5.1 Hz), 1.4~1.7 (5H, m), 1.75~2.0 (3H, m), 2.09 (1H, m), 2.25 (1H, m), 2.30 (6H, s), 2.35 (1H, d, J=12.6 Hz), 2.5 (1H, m), 2.69 (1H, d, J=12 Hz), 2.80 (1H, m), 2.88 (1H, d, J=12.0 Hz), 3.04 (1H, d, J=9.0 Hz), 3.28 (1H, dd, J=6.0 and 10.8 Hz), 3.30 (3H, s), 3.52 (1H, m), 3.6~3.7 (2H, m), 4.03 (2H, m), 4.25 (1H, d, J=3.6 Hz), 4.5 (1H, d, J=8.7 Hz), 4.9 (3H, m); ^{13}C NMR ($CDCl_3$) δ 9.5, 11.23, 11.66, 14.60, 18.21, 21.25, 21.54, 22.19, 26.80, 28.87, 32.0, 35.04, 35.5, 40.35, 44.87, 49.29, 50.33, 54.53, 59.0, 65.28, 66.15, 69.13, 70.89, 72.65, 75.56, 75.82, 77.19, 77.42, 79.38, 79.59, 83.52, 96.27, 102.90, 126.99, 128.37, 128.27, 128.48, 139.86, 177.10; IR ($CDCl_3$) cm^{-1} 2920, 2160, 1720, 1600, 1450, 1375, 1160, 1100, 1050, 1000; MS *m/z* 840 $(M+H)^+$.

Anal Calcd for $C_{44}H_{77}N_3O_{12}\cdot 2H_2O$: C 60.32, H 9.32, N 4.80.
Found: C 60.68, H 8.93, N 4.80.

Compound **7** (43.5 mg, 44%) was also obtained as a white solid: $[\alpha]_D^{25}$ −29.08° (*c* 0.95, MeOH); ^1H NMR (DMSO) δ 0.78 (3H, t, J=6.9 Hz), 0.99 (3H, d, J=6.3 Hz), 1.02 (6H, d, J=6.3 Hz), 1.10 (3H, d, J=6.0 Hz), 1.12 (1H, m), 1.15 (3H, s), 1.19 (3H, d, J=5.7 Hz), 1.3 (3H, s), 1.4~1.6 (4H, m), 1.65 (1H, m), 1.7~1.9 (2H, m), 2.05 (1H, m), 2.2 (1H, m), 2.6 (6H, s), 2.61 (1H, m), 2.75 (1H, d, J=9.0 Hz), 2.8 (1H, m), 2.9 (1H, d, J=9.0 Hz), 3.05 (1H, m), 3.15 (1H, m), 3.35 (1H, m), 3.4 (1H, m), 3.62 (1H, m), 4.05 (2H, m), 4.32 (1H, d, J=6.0 Hz), 4.40 (1H, d, J=8.7 Hz), 5.2 (1H, m); ^{13}C NMR (DMSO) δ 9.66, 10.84,

11.21, 15.67, 18.49, 18.54, 20.88, 20.89, 22.55, 28.0, 29.1, 31.0, 32.5, 34.5, 35.0, 38.5, 41.07, 41.2, 44.13, 48.85, 61.0, 64.25, 64.86, 66.32, 69.20, 72.55, 73.32, 74.70, 75.70, 77.29, 79.19, 82.96, 96.03, 100.98, 173.92; IR (KBr) cm^{-1} 2950, 1730, 1620, 1500, 1460, 1380, 1160, 1110, 1080, 1050, 1010; MS *m/z* 750 $(M+H)^+$.

(9*R*)-21-(*N*-Benzyl-*N*-methylamino)-9-deoxo-9-(*N*,*N*-dimethylamino)erythromycin A (**8**)

Glacial acetic acid (118 μl) was added to a stirring solution of **6** (68 mg, 0.081 mmol) in 5 ml acetonitrile at room temperature. Formalin (37%, 121 μl) was added *via* syringe. Sodium cyanoborohydride (80 mg, 1.22 mmol) was added and the reaction stirred for 14 hours. The reaction mixture was diluted with MeOH and silica gel (200 mg) added. The solvent was removed under reduced pressure, the residue charged onto a silica gel column and eluted with the solvent system; 5% MeOH, 0.5% NH_4OH in CH_2Cl_2 followed by 10% MeOH, 1% NH_4OH in CH_2Cl_2, to yield 66 mg (92%) of **8** as a white solid: $[\alpha]_D^{25}$ −38.2° (*c* 1.2, MeOH); δ 0.81 (3H, t, *J*=6.0 Hz), 1.09 (3H, d, *J*=5.7 Hz), 1.12 (3H, d, *J*=5.7 Hz), 1.21 (3H, d, *J*=6.0 Hz), 1.22 (3H, s), 1.24 (3H, d, *J*=6.0 Hz), 1.25 (3H, d, *J*=4.2 Hz), 1.30 (3H, d, *J*=7.5 Hz), 1.56 (1H, dd, *J*=4.2 and 15 Hz), 1.6~1.72 (4H, m), 1.8~1.94 (3H, m), 2.05 (1H, m), 2.22 (1H, dd, *J*=8.1 and 10.5 Hz), 2.28 (3H, s), 2.30 (9H, s), 2.35 (1H, d, *J*=15 Hz), 2.4~2.55 (3H, m), 2.65 (1H, m), 2.75 (1H, s), 3.05 (1H, dd, *J*=9.0 and 9.3 Hz), 3.29 (1H, dd, *J*=6.6 and 10.5 Hz), 3.31 (3H, s), 3.48~3.8 (4H, m), 4.02 (1H, m), 4.35 (1H, b), 4.5 (1H, d, *J*=7.5 Hz), 4.8 (1H, b), 5.1 (2H, dd, *J*=3.0 and 9.0 Hz), 7.26~7.4 (5H, m); ^{13}C NMR ($CDCl_3$) δ 10.4, 11.8, 11.9, 12.1, 17.98, 18.0, 21.25, 21.60, 23.31, 28.68, 33.31, 34.83, 40.37, 43.98, 44.31, 44.32, 44.50, 49.39, 58.64, 64.11, 65.48, 65.89, 69.51, 70.69, 72.79, 75.30, 77.20, 77.90, 80.0, 95.90, 103.09, 127.31, 128.39, 129.06, 138.48, 176.65; IR ($CDCl_3$) cm^{-1} 2940, 2900, 1730, 1600, 1450, 1380, 1180, 1160, 1110, 1050, 1010;
MS *m/z* 882 $(M+H)^+$ HR-MS Calcd for $C_{47}H_{84}N_3O_{12}(M+H)^+$ 882.6055.
Found 882.6076.

(9*R*)-9-Deoxo-9-(*N*,*N*-dimethylamino)-21-(*N*-methylamino)erythromycin A (**9**)

Palladium hydroxide (50 mg) was added, under nitrogen, to a stirring solution of **8** (46 mg, 0.052 mmol) in 5 ml MeOH. The mixture was hydrogenated at 1 atmosphere for 5 hours. The catalyst was filtered through Celite and washed repeatedly with excess CH_2Cl_2 and MeOH. The combined filtrate and washings was concentrated under reduced pressure and redissolved in 5% NaH_2PO_4 solution (15 ml). The solution was adjusted to pH 10 with NH_4OH and extracted with ethyl acetate (3×15 ml). The combined organic extracts was washed with brine (20 ml), dried ($MgSO_4$) and concentrated. The residue was chromatographed over silica gel (10% MeOH, 1% NH_4OH in CH_2Cl_2) to yield 25 mg (61%) of **9** as a white solid: $[\alpha]_D^{25}$ −34.6° (*c* 1.2, MeOH); ^1H NMR ($CDCl_3$) δ 0.91 (3H, t, *J*=7.4 Hz), 0.97 (1H, m), 1.11 (9H, d, *J*=7.0 Hz), 1.20 (3H, d, *J*=6.9 Hz), 1.23 (6H, d, *J*=5.0 Hz), 1.29 (3H, s), 1.31 (3H, s), 1.32 (3H, d, *J*=6.6 Hz), 1.35~1.8 (7H, m), 1.9 (1H, m), 2.25 (1H, m), 2.29 (6H, s), 2.34 (1H, m), 2.41 (3H, s), 2.51 (6H, s), 2.62 (1H, d, *J*=12.5 Hz), 2.71 (1H, m), 2.92 (1H, d, *J*=12.1 Hz), 3.01 (1H, d, *J*=8.8 Hz), 3.25 (1H, dd, *J*=7.4 and 10.7 Hz), 3.32 (3H, s), 3.50~3.6 (2H, m), 3.71 (1H, s), 4.05 (1H, m), 4.3 (1H, m), 4.45 (1H, d, *J*=6.0 Hz), 4.87~4.90 (2H, m); ^{13}C NMR ($CDCl_3$) δ 9.81, 11.43, 11.67, 13.92, 18.08, 19.0, 21.26, 21.58, 22.60, 28.86, 33.18, 34.94, 37.17, 38.50, 40.40, 42.20, 43.91, 44.66, 49.38, 53.55, 65.47, 66.13, 69.43, 70.80, 72.08, 72.76, 75.68, 76.35, 77.24, 77.69, 78.90, 79.71, 85.0, 96.04, 103.19, 177.17; IR ($CDCl_3$) cm^{-1} 2910, 2900, 1730, 1600, 1450, 1380, 1160, 1105, 1090, 1060, 1050, 1010; MS *m/z* 793 $(M+H)^+$.

(9*R*)-9-Deoxo-9,21-di-(*N*,*N*-dimethylamino)erythromycin A (**10**)

Glacial acetic acid (98 μl, 1.34 mmol) and formalin (100 μl, 1.34 mmol) were added to a stirring solution of **7** (50 mg, 0.067 mmol) in 5 ml acetonitrile. Sodium cyanoborohydride (88 mg, 1.34 mmol), was added and the solution stirred at room temperature for 24 hours. Methanol (5 ml) and silica gel (200 mg) were added and solvent removed *in vacuo*. The residue was charged onto a column of silica gel and eluted with the solvent system; 5% MeOH, 0.5% NH_4OH in CH_2Cl_2 followed by 10% MeOH, 1% NH_4OH in CH_2Cl_2, to yield 58 mg of partially purified material. The material was again chromatographed on silica gel (5% MeOH, 0.5% NH_4OH in CH_2Cl_2) to give 10 mg (18%) of **10** as a white solid: $[\alpha]_D^{25}$ −19.28° (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.96 (3H, t, *J*=6.3 Hz), 1.09 (3H, d, *J*=7.22 Hz), 1.13 (6H, d, *J*=7.0 Hz), 1.21 (3H, d, *J*=6.3 Hz), 1.22 (3H, s), 1.23 (3H, d, *J*=6.0 Hz), 1.28 (3H, s), 1.30 (3H, d, *J*=6.0 Hz), 1.31 (1H, m), 1.5~1.71 (5H, m), 1.78~1.91 (3H, m), 2.2 (1H, m), 2.3 (6H, s), 2.35 (1H, m), 2.40 (6H, s), 2.50

(6H, s), 2.55 (2H, m), 2.65 (1H, m), 2.75 (1H m), 3.05 (1H, m), 3.28 (1H, dd, J=5.9 and 10.5 Hz), 3.31 (3H, s), 3.48~3.65 (3H, m), 4.02 (1H, n), 4.3 (1H, m), 4.5 (1H, d, J=7.2 Hz), 4.8 (1H, d, J=3.3 Hz), 5.05 (1H, dd, J=3.0 and 9.0 z); ^{13}C NMR ($CDCl_3$) δ 9.95, 11.79, 13.0, 17.92, 19.1, 21.20, 21.58, 23.16, 28.69, 33.31, 34.80, 40.36, 2.90, 43.71, 43.76, 44.24, 47.65, 49.35, 59.93, 65.44, 65.92, 69.47, 70.71, 72.78, 75.29, 76.85, 77.21, 77.70, 7.90, 79.67, 85.0, 95.54, 102.98, 176.56; IR ($CDCl_3$) cm^{-1} 2960, 2910, 2810, 1730, 1600, 1460, 1380, 116 1050, 1010; MS m/z 806 $(M+H)^+$.

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