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THE CYCLOCONDENSATION REACTION OF 1-BENZOYLOXY-2-*TERT*-BUTYL-DIMETHYLSILYLOXY-4-METHOXY-1,3-BUTADIENE WITH *N,O*-PROTECTED D-THREONINALS AND D-*ALLO*-THREONINALS‡

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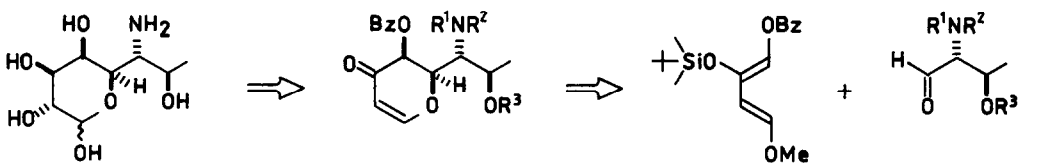
Abstract. The zinc bromide-catalyzed reaction of 1-benzoyloxy-2-*tert*-butyldimethylsilyloxy-4-methoxy-1,3-butadiene (**3**) with *N*-carbobenzoxy-*O*-protected-D-*allo*- (**4**) and -D-threoninal (**9**) was studied. Pyrones **7a** and **12a** were transformed into diastereoisomers of lincosamine (**16** and **19**).

Introduction

During our long term study directed toward the total synthesis of lincosamine we turned our attention to the application of the Diels-Alder reaction between a 1,2,4-trioxygenated derivative (**3**) of Danishefsky's diene and α-amino aldehydes **4** obtained from D-*allo*-threonine.[1,2]This approach provides an easy solution to the problem connected with the functionalization of side-chain of the target.[3]

Scheme 1



1 **2** **3** **4**

Results

We first studied the influence of the β-protecting group of the dienophile on the stereochemical course of the [4+2] cycloaddition. As a result of the reaction between diene **3** and D-threonine and D-*allo*-threonine derived aldehydes **4a**, **4b**, **9a** and **9b** four diastereoisomeric products are possible to be formed, two *cis*-diastereoisomers (**5** and **7**, **10** and **12**) by *endo* addition, and two *trans*-diastereoisomers (**6** and **8**, **11** and **13**) by *exo* addition. *Re*-addition leads to *erytro*-products (**5** and **6**, **10** and **11**), while *si*-addition gives *threo*-adducts (**7** and **8**, **12** and **13**). The predominance of α-chelating interactions in the zinc bromide-catalyzed cyclocondensation step resulted in high *threo*-selectivity (Scheme 2, Table 1). For the stereochemical models analysis see ref. 2.

Scheme 2

HNCbz
OR
O
H
1. ZnBr2
2. TFA
BzO HNCbz
OR
O
O
4a : R = TBDPS
4b : R = BOM
5a
5b
6a
6b
7a
7b
8a
8b
OBz
OMe
SiO
3
9a : R = TBDPS
9b : R = BOM
10a
10b
11a
11b
12a
12b
13a
13b

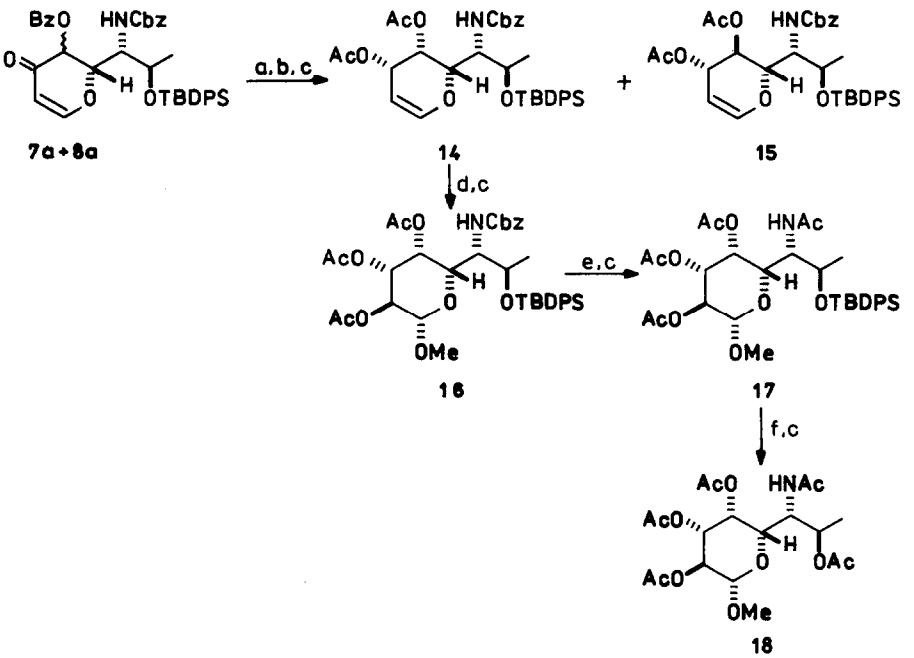
Table 1

The reaction of diene **3** with aldehydes **4a**, **4b**, **9a**, and **9b**

Entry	Aldehyde	Equivalents of $ZnBr_2$	Yield [%]	Diastereoisomeric ratio			
				4S:5R	*4R:5R*	*4R:5S*	*4S:5S*
				5, 10	**6, 11**	**7, 12**	**8, 13**
1	**4a**	1	60	---	---	2.0	1.0
2	**4b**	1	55	0.2	0.1	0.1	1.0
3	**4b**	2	50	0.6	0.3	1.5	1.0
4	**9a**	1	65	---	---	3.0	1.0
5	**9b**	1	67	---	---	4.6	1.0

To show the utility of this synthetic approach, adduct **7a** was transformed into diastereoisomeric analogue (**18**) of lincosamine (Scheme 3).

Scheme 3



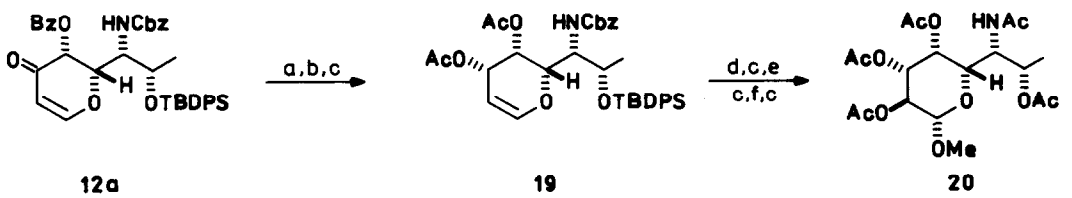
Scheme 3. a: $NaBH_4$, $CeCl_3.7H_2O$, MeOH, -78°C, 1 h; b: NH_3, MeOH, RT, 24 h; c: Ac_2O, Et_3N, $DMAP_{cat}$, CH_2Cl_2, RT, 1 h; d: mCPBA, MeOH, -20°C, 4 days; e: H_2, Pd-C, EtOAc, RT, 1 h; f: Bu_4NF, THF, RT, 10 h.

Functionalization of the dihydropyran ring, leading to the product of galacto configuration[4], was achieved by diastereoselective reduction of the carbonyl group, followed by debenzylation and acetylation of the resulting diol, to afford diacetate **14** and **15**. Compound **14** was then epoxidized, using m-chloroperbenzoic acid in methanol

and acetylated to yield the protected analogue of lincosamine **16**, which, for analytical purposes, was transformed into the peracetyl derivative **18**. The absolute configuration of compound **18** was confirmed by X-ray analysis.[1]

Using a similar approach, compound **12a** was transformed into the pentaacetyl derivative of lincosamine **20.**

Scheme 4



Scheme 4. a: $NaBH_4$, $CeCl_3.7H_2O$, MeOH, -78 °C, 1 h; b: NH_3, MeOH, RT, 24 h; c: Ac_2O, Et_3N, $DMAP_{cat}$, CH_2Cl_2, RT, 1 h; d: mCPBA, MeOH, -20 °C, 4 days; e: H_2, Pd-C, EtOAc, RT, 1 h; f: Bu_4NF, THF, RT, 10 h.

Experimental Section:

^1H NMR spectra were recorded at 500 MHz with a Bruker AM 500 spectrometer in $CDCl_3$ as solvent. ^{13}C NMR spectra were measured at 125 MHz with a Bruker AM 500 spectrometer. Infrared spectra were recorded on a Beckman IR-4240 spectrometer. Optical rotations were determined with a Perkin-Elmer 141 polarimeter.

Column chromatography was carried out with Merck Kieselgel 60 (230-400 mesh), according to Still's procedure.[5] All chromatographic separations were monitored by TLC analyses, performed on Merck DC Alufolien Kieselgel 60F-254. Yields are reported for chromatographically pure compounds.

D-*allo*-Threoninals **4a, 4b** and D-threoninals **9a, 9b** were prepared as described previously.[2] Diene **3** was prepared according to a literature method.[5]

Adducts 7a and 8a. Typical procedure

Aldehyde **4a** (950 mg, 2 mmol) and anhydrous zinc bromide (450 mg, 2 mmol) in dry THF (10 mL) were stirred at room temperature for 1 h. To the homogenous solution, diene **3** (1.3 g, 4 mmol) was added, and the reaction mixture was stirred at room temperature for 48 h. Trifluoroacetic acid (1 mL) was added and after an additional 5 min stirring the solution was partioned between diethyl ether (30 mL) and a saturated sodium bicarbonate solution (30 mL). The organic layer was dried ($MgSO_4$), evaporated and the residue was chromatographed (hexane-ethyl acetate 6:4) to afford an unseparable mixture (2:1) of pyrones **7a** and **8a** (800 mg, 60 % yield), oil. IR (film): 3350, 1750, 1450, 1030, 700 cm^{-1}. Anal. calcd for $C_{39}H_{41}NO_7Si$: C 70.56; H 6.23; N 2.11. Found: C 70.21; H 6.27; N 2.08. **7a**: ^1H NMR[6]: 7.02(d, J=5.7 Hz, 1H); 5.77(d, J=1.0 Hz, 1H); 5.50(d, J= 5.7 Hz, 1H); 5.11(d, J= 1.0 Hz, 1H); 4.12(d, J= 8.1Hz, 1H); 3.87(dq, J= 8.1, 6.1 Hz, 1H); 1.08(d, J= 6.1 Hz, 3H). **8a**: ^1H NMR[6]: 7.00(d, J=6.0 Hz, 1H); 5.70(d, J= 12.0 Hz, 1H); 5.43(d, J= 6.0 Hz, 1H); 4.79(m, 1H); 4.10(m, 1H); 3.95(m, 1H); 1.12(d, J= 6.1 Hz, 3H).

Using this procedure aldehyde **4b** (357 mg, 1 mmol) was transformed into an unseparable mixture (0.2: 0.1: 1.5: 1.0) of adducts **5b, 6b, 7b, 8b** (300 mg, 55% yield).

Oil, IR (film): 3350, 1730, 1450, 1030, 700. Anal. Calcd for $C_{31}H_{31}NO_8$: C 68.24; H 5.73; N: 2.57. Found: C: 68.30; H: 5.83; N:2.60.

Table 2. Proton NMR chemical shifts of adducts **5b, 6b, 7b, 8b.**

	H1	H2	H3	H4	H5	H6	H7	H8
5b	7.0	5.53	---	5.79	5.02	4.18	3.85	1.24
6b	7.0	5.46	---	5.84	5.05	4.03	3.83	1.30
7b	7.0	5.51	---	5.82	5.05	4.19	3.89	1.26
8b	7.0	5.43	---	5.73	5.15	4.11	3.94	1.30

Only the skeleton proton signals are presented; the signals originated from protons of the protecting groups are omitted.

Table 3. Spin-spin coupling constants observed for the skeleton protons of adducts **5b, 6b, 7b, 8b.**

	$J_{1,2}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$
5b	6.1	3.4	2.0	7.0	6.2
6b	6.0	12.1	ND	ND	6.0
7b	6.2	3.5	0.5	7.8	6.4
8b	5.8	13.5	0.0	9.8	6.2

ND - not determined

Using the same procedure aldehyde **9a** 475 mg, 1 mmol) was transformed into 353 mg of adduct **12a** and 75 mg of adduct **13a** (65% yield).

12a: mp 117.0-117.5°C; $[\alpha]^{20}$ +46.6° (c 0.9, $CHCl_3$); IR (film): 3350, 1740, 1450, 1090, 690. Anal. calcd for $C_{39}H_{41}NO_7Si$: C 70.56; H 6.23; N 2.11. Found: 70.56; H: 6.16; N:2.02. ^1H NMR: 8.05-7.20(m, 21H); 5.52(d, J=6.1 Hz, 1H); 5.26(d, J= 10.0 Hz, 1H); 5.25(bs, 1H); 5.03(d_{AB}, J=12.1 Hz, 1H); 4.87(d_{AB}, J=12.1 Hz, 1H); 4.53(dd, J=8.1, 0.5 Hz, 1H); 4.18(q, J=6.3 Hz, 1H); 4.04(dd, J=10.0, 8.1 Hz, 1H); 1.05(s, 9H); 1.04(d, J=6.3 Hz, 3H).

13a: oil, $[\alpha]^{20}$ -103.5° (c 2, $CHCl_3$); IR (film): 3350, 1730, 1450, 1100, 690. Anal. calcd for $C_{39}H_{41}NO_7Si$: C: 70.56; H: 6.23; N: 2.11. Found: C: 70.54; H: 6.28; N: 2.10. ^1H NMR: 8.05-7.20(m, 21H); 5.68(d, J=13.0 Hz, 1H); 5.48(d, J= 5.9 Hz, 1H); 5.18-4.90(m, 4H); 4.17(m, 1H); 4.08(m, 1H); 1.15(d, J=6.3 Hz, 3H); 1.04(s, 9H).

Using the same procedure aldehyde **9b** (373mg, 1mmol) was transformed into (4.6 : 1.0) mixture of adducts **12b** and **13b** (353mg, 67% yield).

Oil, IR (film): 3350, 1740, 1480, 1050, 700. Anal. calcd for $C_{31}H_{31}NO_8$: C 68.24; H 5.73; N 2.57. Found: C 68.38; H 5.89; N 2.45.

12b: ^1H NMR: 8.05-7.20 (m, 15H); 7.49 (d, J=6.0 Hz, 1H); 5.71 (bd, J=1.2 Hz, 1H); 5.55 (dd, J=6.0, 1.0 Hz, 1H); 5.17 (d, J=9.9 Hz, 1H); 5.08 (d, J=12.3 Hz, 1H); 4.96 (d, J=12.3 Hz, 1H); 4.78 (d, J=7.0 Hz, 1H); 4.74 (d, J= 7.0 Hz, 1H); 4.58 (m, 3H); 4.14 (m, 1H); 1.19 (d, J=6.2 Hz, 3H).

13b: ^{1}H NMR: 8.06-7.20 (m, 16H); 5.76 (d, J=13.1 Hz, 1H); 5.50(d, J=5.7 Hz, 1H); 5.15 (d, J=8.7 Hz, 1H); 5.10 (dAB, J= 12.0 Hz, 1H); 5.06 (dAB, J=12.0 Hz, 1H); 4.87(dd, J=7.0 Hz, 1H); 4.78(d, J=7.0 Hz, 1H); 4.72 (d, J=7.0 Hz, 1H); 4.55(bs, 2H); 4.16 (m, 1H); 4.08 (m, 1H); 1.29 (d, J=6.2 Hz, 3H).

Synthesis of diastereoisomer 18 of lincosamine.

To a solution of pyrones **7a** and **8a** (**7a**:**8a** 2:1; 660 mg, 1 mmol) and cerium (III) chloride heptahydrate (1.5 mmol, 558.8 mg) in methanol (10 mL) at -78 °C, under argon, sodium borohydride (1.5 eq, 56.7 mg) in absolute ethanol (2 mL) was added. After stirring at -78 °C for 1 h, the reaction mixture was allowed to warm to 0°C, whereupon it was diluted with diethyl ether (40 mL) and quenched with a pH 7 buffer (20 mL). The reaction mixture was transferred to a separatory funnel and the water layer was extracted with ether (3x20 mL). The organic layers were combined, dried over $MgSO_4$, concentrated in vacuo. The oily residue was dissolved in metanol saturated with ammonia and the reaction mixture was left overnight at room temperature (20 °C). Then the solvent was evaporated and the oily residue was dissolved in methylene chloride (10 mL). Triethyl amine (202 mg, 278 µL, 2 mmol) was added, followed by acetic anhydride (153 mg, 141 µL, 1.5 mmol) and a catalytic amount of DMAP (4-dimethylaminopyridine). After 0.5 h, the solvent was evaporated and the oily residue purified by column chromatography (hexane - ethyl acetate; 85:15 to 8:2) to afford 340 mg of diastereoisomerically pure diacetate **14** and 170 mg of pure diacetate **15** (80 % overall yield).

Diacetate **14**: oil, $[\alpha]^{20}$ +1.5° (c 4, $CHCl_3$); Anal. calcd for $C_{36}H_{43}NO_8Si$: C 66.95; H 6.71; N 2.17. Found: C 66.83; H 6.62; N 2.09. IR(film): 3350, 1740, 1470, 120, 680. ^{1}H NMR: 7.66-7.24(m, 15H); 6.35 (d, J= 6.1 Hz, 1H); 5.47 (m, 2H); 5.08 (d, J=12.1 Hz, 1H); 4.99 (d, J=12.1 Hz, 1H); 4.97 (m, 1H); 4.58 (m, 2H); 3.82 (m, 2H); 1.98 (s, 3H); 1.88 (s, 3H); 1.03 (d, J=6.2 Hz, 3H); 1.02 (s, 9H).

Diacetate **15**: oil, $[\alpha]^{20}$ +4.2° (c 2, $CHCl_3$); Anal. calcd for $C_{36}H_{43}NO_8Si$: C 66.95; H 6.71; N 2.17. Found: C 66.89; H 6.58; N 2.21. IR(film): 3320, 1780, 1470, 1040, 700. ^{1}H NMR: 7.69-7.25 (m, 15H); 6.24 (d, J=5.8 Hz, 1H); 5.52 (dd, J=6.2, 0.5 Hz, 1H); 5.22 (dd, J=11.0, 6.2 Hz, 1H); 5.11 (d, J=8.1 Hz, 1H); 4.95 (d, J=8.1 Hz, 1H); 4.77 (d, J= 10.6 Hz, 1H); 4.71 (dd, J=5.9, 0.5 Hz, 1H); 4.58 (d, J=11.0Hz, 1H); 3.94 (dd, J=10.4, 9.2 Hz, 1H); 3.84 (dq, J=9.2, 6.2 Hz, 1H); 2.14 (s, 3H); 2.03 (s, 3H); 1.06 (d, J=6.2 Hz, 3H); 1.03 (s, 9H).

Triacetate 16.

To a cold solution (-20 °C) of diacetate **14** (130 mg, 0.2 mmol) in methanol (1 mL) was added solid m-chloroperbenzoic acid (85%, 120 mg, 0.6 mmol). After 7 days at room temperature, methanol was evaporated and the residue was acetylated under standard conditions (acetic anhydride (1.2 eq), triethylamine (1.5 eq), methylene chloride 5 mL, and a catalic amount of DMAP, room temperature for 0.5 h). After completion of the reaction (TLC; hexane - ethyl acetate 1:1), solvent was evaporated and the oily residue was purified by column chromatography (hexane - ethyl acetate; 7:3 to 6:4) to afford 124 mg (85% yield) of compound **16** and 15 mg of its α-anomer.

16: mp 51-53°C; $[\alpha]^{20}$ +11.3° (c 3, $CHCl_3$). Anal. calcd for $C_{39}H_{49}NO_{11}Si$: C 63.65; H 6.71; N 1.90. Found: C 63.51; H 6.80; N 2.00. ^{1}H NMR: 7.70-7.20(m,15H); 5.39(d, J= 3.5 Hz, 1H); 5.19(m,1H); 5.15-4.95(m,3H); 4.88(dd, J= 10.4, 3.5 Hz, 1H); 4.09(bs,1H); 4.00(d, J=7.6 Hz, 1H); 3.75(m,2H); 3.27(s,3H); 2.05(s,3H); 1.96(s,3H); 1.88(s,3H); 1.06(s,9H); 1.05(d, J= 6.4 Hz, 3H).

Tetraacetate 17.

Compound **16** (74 mg, 0.1 mmol) dissolved in methanol (5 mL) was reduced with hydrogen in the presence of 10% palladium-on-charcoal (15 mg) for 1 h; the catalyst was filtered off and the solvent was evaporated. The residue was acetylated under standard conditions to give 55 mg (85 % yield) of product **17**: mp 197-199.0 °C; $[\alpha]^{20}$ +22.5° (c 2.5, $CHCl_3$). Anal. calcd for $C_{33}H_{45}NO_{10}Si$: C 61.56; H 7.04; N 2.17. Found: C 61.44; H 7.16; N 2.17. IR (KBr): 3320, 1740, 1060. ^1H NMR: 7.70-7.36(m,10H); 5.80(d, J= 9.3 Hz, 1H); 5.39(d, J= 2.7 Hz, 1H); 5.10(dd, J= 10.8, 8.0 Hz, 1H); 4.90(dd, J= 10.5, 3.5 Hz, 1H); 4.13(s,1H); 4.04(m,2H); 3.74(m,1H); 3.31(s,3H); 2.06(s,3H); 2.03(s,3H); 1.97(s,3H); 1.07(d, J= 6.7 Hz, 3H); 1.07(s,9H).

Pentaacetate 18.

Tetraacetate **17** (45 mg, 0.07 mmol) was treated with tetrabutylammonium fluoride (100 mg, 0.3 mmol) in THF (0.5 mL). After 15 h the solvent was evaporated and the oily residue was acetylated. Chromatographic purification (hexane - ethyl acetate; 1:9) afforded 23 mg (76 % yield) of the crystalline product **18**. mp 184.5°C, $[\alpha]^{20}$ +54.8° (c 1.1, $CHCl_3$). Anal. calcd for $C_{19}H_{29}NO_{11}$: C 51.00; H 6.53; N 2.93. Found: C 50.96; H 6.34; N 2.93. IR (KBr): 3300, 1750, 1060. 1H NMR: 5.92(d, J= 8.7 Hz, 1H); 5.42(dd, J= 3.5, 0.5 Hz, 1H); 5.14(dd, J= 10.4, 8.1 Hz, 1H); 5.01(dd, J= 10.4, 3.5 Hz, 1H); 4.93(dq, J= 8.1, 6.4 Hz, 1H); 4.32(d, J=8.1 Hz, 1H); 4.26(ddd, J= 8.7, 8.1, 0.5 Hz, 1H); 3.54(s,3H); 2.09(s,3H); 2.06(s,3H); 2.05(s,3H); 2.03(s,3H); 1.97(s,3H); 1.22(d, J= 6.4 Hz, 3H). ^{13}C NMR: 170.3, 170.1, 169.7, 169.5, 169.3, 146.7, 102.6, 102.5, 102.3, 70.7, 70.4, 70.3, 69.8, 69.4, 69.3, 69.2, 68.5, 57.4, 52.2, 23.4, 21.2, 20.7, 20.6, 20.5, 18.0, 16.6.

Synthesis of diastereoisomer 20 of lincosamine.

Diacetate 19.

Using the same method as for compound **14**, pyrone **12a** (663 mg, 1 mmol) was transformed into diacetate **19** (547 mg, 84.8 % yield). **19**: an oil. Anal. calcd for $C_{36}H_{43}NO_8Si$: C 66.95; H 6.71; N 2.17. Found: C 66.89; H 66.78; N 2.23. IR (film): 3350, 1750, 1460, 1050, 700. ^1H NMR: 7.70-7.20(m,15H); 6.46(d, J= 6.3 Hz, 1H); 5.38(dd, J= 4.8, 2.0 Hz, 1H); 5.19(dd, J= 4.8, 0.5 Hz, 1H); 5.15(bs, 2H); 5.14(dd, J= 2.0, 1.0 Hz, 1H); 4.62(dd, J= 6.3, 1.0 Hz, 1H); 4.17(d, J= 7.1 Hz, 1H); 4.03(qd, J= 5.9, 2.2 Hz, 1H); 3.74(ddd, J= 7.1, 2.2, 0.5 Hz, 1H); 2.01(s,3H); 2.00(s,3H); 1.05(s,9H); 1.01(d, J= 5.9 Hz, 3H).

Pentaacetate 20.

Using the above procedure compound **19** (323 mg, 0.5 mmol) was transformed into the peracetyl analogue of lincosamine **20** (89 mg, 20 % yield). mp 186.0-188.0°C.$[\alpha]^{20}$ +14.9° (c 1.4, $CHCl_3$). Anal. calcd for $C_{19}H_{29}NO_{11}$: C 51.00; H 6.53; N 3.13. Found: C 51.17; H 6.41; N 3.02. IR (KBr): 3300, 1755, 1070. ^1H NMR: 5.93(d, J= 8.0 Hz, 1H); 5.42(d, J= 3.2 Hz, 1H); 5.16(dd, J= 10.6, 8.0 Hz, 1H); 5.06(qd, J= 6.5, 3.3 Hz, 1H); 5.01(dd, J= 10.6, 3.2 Hz, 1H); 4.36(d, J= 8.0 Hz, 1H); 4.23(ddd, J= 8.0, 3.3, 1.0 Hz, 1H); 3.86(s, 1H); 2.07(s, 3H); 2.06(s, 3H); 2.05(s, 3H); 2.04(s, 3H); 1.96(s, 3H); 1.20(d, J= 6.5 Hz, 3H).

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