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SECONDARY METABOLITES BY CHEMICAL SCREENING[1]-6.

CLEAVAGE OF ELAIOPHYLIN AND TRANSFORMATION INTO A SPIROKETAL BUILDING BLOCK

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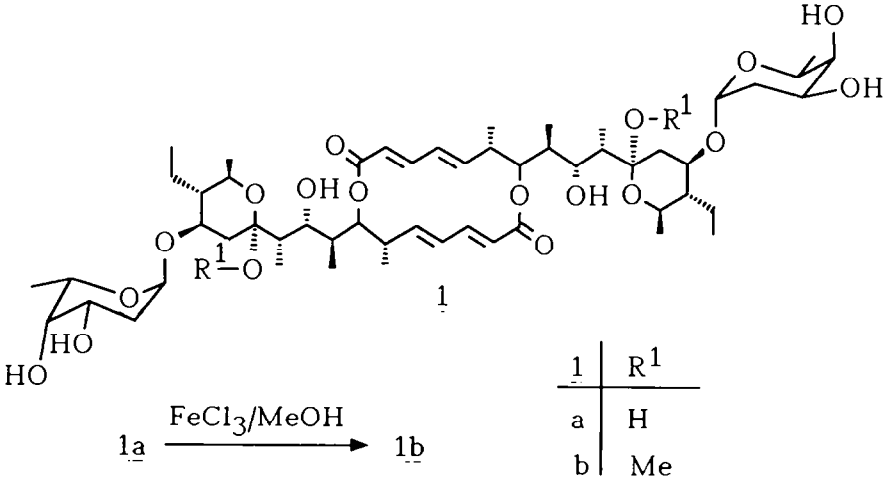
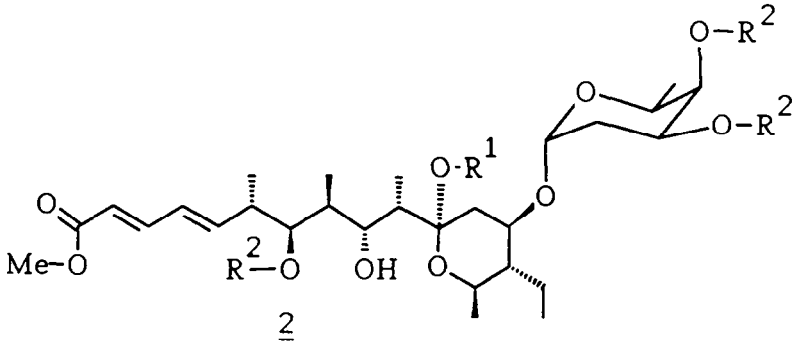
Abstract: A novel methodology for the controlled basic cleavage of the macrodiolide antibiotic elaiophylin (**1a**) to the seco-acid ester **2a** and further transformation into the spiroketal building blocks **4** and **5** under Lewis acid catalysis has been developed.

Elaiophylin (**1a**) represents a biologically interesting member of the family of macrodiolide antibiotics[2] and exhibits anthelmintic activity in vivo.[3] During our semisynthetic work on this sensitive compound concerning structure-activity relationships,[4] we learned that the natural product **1a** itself is unsuitable for preparation of various derivatives, especially if reagents more basic than pyridine (for acylation[4]) or aqueous hydrogencarbonate (for sugar elimination at 60°C) are required.[5]



Scheme 1

Our investigations were directed to evaluate speculations about t 1,7-dioxaspiro-(5,5)-undecane moiety eventually responsible for the biol gical activity of the various milbemycin and avermectin macrolides.[6] fact, **1a** can be easily cleaved into the seco macrodiolide in a one-flas procedure and subsequently transformed into such a spiroketal system.



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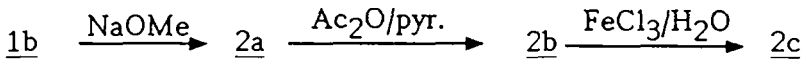

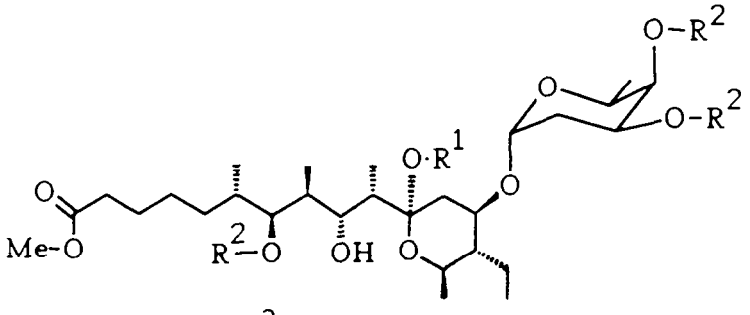

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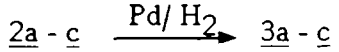
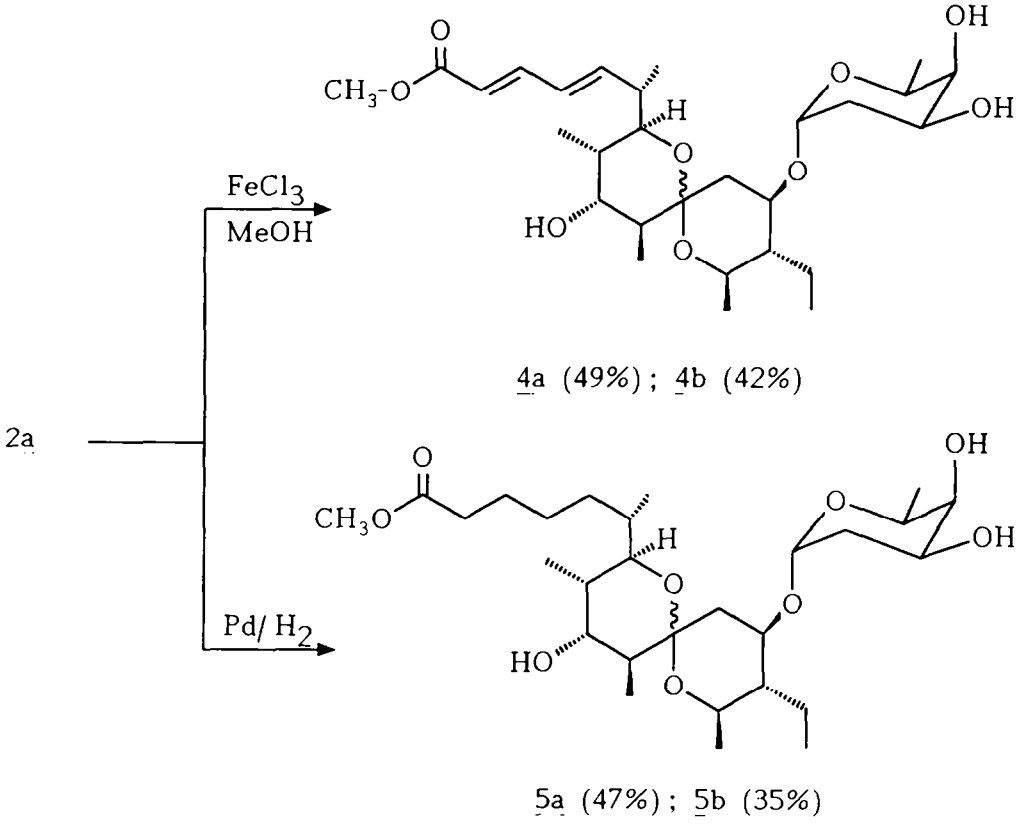


2 or 3	R^1	R^2
a	Me	H
b	Me	Ac
c	H	Ac

Scheme 2

In the first step elaiophylin (**1a**) is protected from retro-aldol cleavage and further side reactions, which otherwise would lead to total decomposition, simply by addition of a small amount (1 - 5% by weight) of iron(III)chloride to a solution of **1a** in dry methanol at room temperature[5] (scheme 1). The 11, 11'-dimethyl ketal **1b** is quantitatively formed within a few seconds and may be isolated in 92% yield by direct crystallization from the cold concentrated solution. The macrodiolide ring is cleaved with 1N sodium methoxide in methanol. After 1.5 hours at room temperature the reaction is quenched with solid ammonium chloride to afford the elaiophylin seco-acid methylester (**2a**) in 89% isolated yield (scheme 2) as a non-crystalline solid. Seco-ester **2a** was converted to some crystalline derivatives as follows.



Scheme 3

Acylation of **2a** with acetic acid anhydride in pyridine as usu furnishes the triacetate **2b** which can be demethylated in aqueo isopropanol in the presence of catalytic amounts of iron(III)chloride give the triacetate **2c**.

Compound **3a** can be obtained, in moderate yield (31%) from t corresponding octahydro derivative of **1b** by macrodiolide cleavage wi sodium methoxide in methanol (5h at 20°C) in a strictly analogous mann as desribed above.

Upon addition of iron(III)chloride (1 - 5% by weight) to a methanol solution of the seco-ester **2a** within minutes at room temperature, the t epimeric spiroketals **4** are formed (scheme 3). These are easily separat by silica gel column chromatography (with ethyl acetate as eluent) as no crystalline solids (ca. 1/1 ratio of **4a/4b**).

Surprisingly, the analogues spiroketalization reaction occurs when t side chain in **2a** is hydrogenated with active hydrogenation catalys (palladium on charcoal, Merck) in methanol delivering the saturat analogues in a similar ratio (47% and 35% yield)[8] (scheme 3).

Using a less reactive catalyst (Pd/C, 10%, Riedel-de-Haen), howeve gives the expected open chain derivatives **3a** - **3c**. Clearly, the acetat **2b** and **2c** cannot cyclize under either conditions.

Although the literature reports a number of syntheses of the 1, dioxaspiro(5,5)-undecane system, many of which depend on the constructi of a 1,9-dihydroxy-5-oxo-nonane system[7-10], we believe that c methodology represents a mild procedure for selective manipulation of t hemiketal moiety encountered in many other macrolide natural products[2]. is important to note that under these carefully controlled conditions elaborate protective group techniques are required and that the glycosid bonds remain unaffected.

Investigations on the biological activities of all products are und way and will be reported elsewhere.

Because of the complexity and the poor resolution even in high field NMR spectra only the chemical shifts of some characteristic atoms could assigned. The complete assignments of all carbon atoms in the ^{13}C-N spectra are under investigation by means of 2D experiments (H correlation and C-H-shift-correlation) and will be discussed elsewhere[11].

Acknowledgement: We like to thank the Bundesministerium für Forschung u Technologie for financial support and Dr. H. Kluge for valuable NM discussions.

EXPERIMENTAL

Melting points were determined with a Kofler hot stage apparatus and are uncorrected. NMR spectra were recorded on a Bruker AM 300. Chemical shifts are expressed in ppm with TMS as internal standard. IR spectra in pressed KBr discs were recorded on a Perkin-Elmer 197 spectrometer and are expressed in cm^{-1}. The FAB mass spectra were taken by a MS 50 Kratos Analytical (FAB-MS) with 3-nitrobenzyl-alcohol as matrix. Thin layer chromatography (TLC) was carried out on silica gel plates (Merck F_{254}). Optical rotation was measured with a Perkin Elmer spectrometer 241.

11-O-Methyl-seco-elaiophylin methyl ester (2a)

A: 2.15 g (2.04 mmol) of 11,11'-di-O-methylelaiophylin (**1b**)[4] are dissolved at room temp. in 40 ml of a 1N sodium methoxide solution. After 1.5 h, 5.35 g (100 mmol) of ammonium chloride are added in one portion with stirring and the mixture is concentrated to dryness on a rotary evaporator. The residue is stirred in ethyl acetate and precipitated sodium chloride is removed by filtration. The oil remaining after distilling off the solvent is filtered through silica gel using ethyl acetate. The product **2a** can be isolated as a colourless powder, after evaporation of the solvent, by stirring with n-pentane, yield 2.03 g (89%): $[\alpha]_D^{20}$ -45° (c = 1, CH_3OH); Analysis for $C_{29}H_{50}O_{10}$ (558.71): calcd C, 62.3; H, 9.0; found C, 62.1; H, 9.1; FAB MS (KCl matrix) cluster ion $(M+K)^+$ m/e = 596; Characteristic ^{13}C NMR (75,5 MHz, pyridine d_5): δ = 167.5 (1-C), 104.0 (11-C), 94.2 (1'-C); ^1H NMR (300 MHz, pyridine-d_5): δ = 2.8(d, d, 1H, J = 12Hz, J = 4.5Hz, 12-Heq), 3.2(s, 3H, CH_3-acetal), 3.65(s, 3H, CH_3-ester), 3.7(m, 1H, 15-H), 4.05(pseudo s, 1H, 4'-H), 4.1-4.5(m, 5H, 7-H, 9-H, 3'-H, 5'-H, 13-H), 5.2(pseudo s, 1H, 1'-H), 5.7 - 6.5 (m, 3H, H-2, H-4, H-5), 7.4 (m, 1H, H-3).

B: The compound **2a** can also be prepared directly from elaiophylin (**1a**) as follows:

2.10 g (2.04 mmol) of elaiophylin (**1a**) are suspended in 20 ml of anhydrous methanol and 60 mg of anhydrous iron(III)chloride are added. After stirring for 5 min at room temp. 20 ml of a 2 M sodium methoxide solution are added and the product is isolated as described above, yield: 1.80 g (79%).

3',4',7-Tri-O-acetyl-11-O-methyl-seco-elaiophylin methyl ester (2b)

1.12 g (2.01 mmol) **2a** are dissolved in 10 ml of dichloromethane, 10 ml of pyridine and 10 ml of acetic anhydride. The solution is allowed to stand for 14 h at room temp. and diluted with 200 ml of diethyl ether and the organic phase is extracted with saturated aqueous sodium hydrogencarbonate solution until it has a neutral reaction. After drying over sodium sulfate, concentrating and filtering through silica gel with diisopropyl ether, the product **2b** is recrystallized from diisopropyl ether/n-pentane, yield: 0.65 g (45 %); m.p. 164 - 165°C (dec.); $[\alpha]_D^{20}$ -21.2° (c = 1, CH_3OH); Analysis for $C_{35}H_{56}O_{13}$ (684.8): calcd C, 61.4; H, 8.3; found C, 61.7; H, 8.5; IR (KBr): 1740 (acetate), 1725 (methyl ester), 1650/1620 (C=C); Characteristic ^{13}C NMR (pyridine-d_5): δ = 93.9 (1-C), 170.9 , 170.7, 170.0 (OAc), 167.3 (1-C), 103.8 (11-C); ^1H NMR (300 MHz, pyridine-d_5): δ = 2.0(s, 3H, OAc), 2.05(s, 3H, OAc), 2.1(s, 3H, OAc), 2.8(d, d, J = 12Hz, J = 4.5Hz, 1H, 12-Heq), 3.2(s, 3H, CH_3-acetal), 3.7(pseudo s, 4H, CH_3-ester, 15-H), 4.0(m, 1H, 13-H), 4.25(m, 2H, 5'-H, 9-H), 5.15(pseudo s, 1H, 1'-H), 5.5-6.2(m, 6H, 3'-H, 4'-H, 2-H, 4-H, 5-H, 7-H), 7.4(m, 1H, 3-H).

3',4',7-Tri-O-acetyl-seco-elaiophylin methyl ester (2c)

1.37 g (2.00 mmol) of **2b** are dissolved in 10 ml isopropanol and 0.1 of water. 50 mg of iron(III)chloride are added and the mixture is stirr at room temperature until completion of the reaction (TLC checking silica gel using dichloromethane/methanol 40:1) (reaction time about min). After addition of 100 ml of ether, the organic phase is washed twi with 50 ml of sodium hydrogencarbonate solution each time, dried (Na_2SC and concentrated. The product is crystallized from diisopropyl ethe n-pentane, yield: 0.79 g (59 %); mp. 147-148°C (dec.); $[\alpha]_D^{20}$ -59° (c = CH_3OH); Analysis for $C_{34}H_{54}O_{13}$ (670.80): calcd C, 60.9; H, 8.1; fou C, 61.2; H, 8.2; FAB MS (KCl matrix) cluster ion $(M+K)^+$ m/e = 70 Characteristic ^{13}C NMR (pyridine-d_5): δ = 171.1, 170.8, 170.0 (OAc), 167 (1-C), 100.0 (11-C), 93.8 (1'-C); ^1H NMR (300 MHz, pyridine-d_5 δ = 2.8(m, 1H, 12-Heq), 3.65(s, 3H, CH_3-ester), 4.0-4.4(m, 4H, 5'-H, 9- 13-H, 15-H), 5.4-6.0(m, 7H, 1'-H,3'-H 4'-H, 2-H, 4-H, 5-H, 7-H), 7.4(1H, 3-H).

2,3,4,5-Tetrahydro-11-O-methyl-seco-elaiophylin methyl ester (3a)

2.60 g (4.65 mmol) of 11-O-methyl-seco-elaiophylin methyl ester (2 are dissolved in 50 ml of methanol and hydrogenated using 0.20 g of 1 palladium/carbon (Riedel-de-Haen) at normal pressure and room temp. unt the calculated amount of hydrogen has been consumed. After filtering c the catalyst and concentrating, the residue is crystallized from dieth ether/diisopropyl ether, yield: 1.62g (62%); mp. 81°C; Analysis f $C_{29}H_{54}O_{10}$ (562.74): calcd C, 61.9; H, 9.6; found C, 61.7; H, 9.7; FAB (KCl matrix) cluster ion $(M+K)^+$ m/e = 601; Characteristic ^{13}C N (pyridine-d_5): δ = 173.9 (1-C), 104.1 (11-C), 94.2 (1'-C); ^1H N (300 MHz, pyridine-d_5): δ = 2.8(d, d, 1H, J = 12Hz, J = 4.5Hz, 12-Heq 3.2(s, 3H, CH_3-acetale), 3.60(s, 3H, CH_3-ester), 3.7(m, 1H, 15-H 4.15(pseudo s, 1H, 4'-H), 4.25-4.55(m, 5H, 7-H, 9-H, 13-H, 4'-H, 5'-H 5.15(pseudo s, 1H, 1'-H).

3',4',7 -Tri-O-acetyl-11-O-methyl-2,3,4,5-tetrahydro-seco-elaiophylin methyl ester (3b)

0.80 g (1.16 mmol) of **2b** are dissolved in 15 ml of methanol a hydrogenated using 0.10 g of 10% palladium/carbon (Riedel-de-Haen) normal pressure and room temp. until the calculated amount of hydrogen h been taken up. After filtering over Corolite, concentrating and drying vacuo 0.79 g (99%) of product are obtained as a colourless solid: $[\alpha]_D$ -49° (c = 1, CH_3OH); Analysis for $C_{35}H_{60}O_{13}$ (688.85): calcd C, 61.0; 8.8; found C, 61.4; H, 9.0; IR (KBr) 1740 (OAc), 1720 (methyl ester); F MS (KCl matrix) cluster ion $(M+K)^+$ m/e = 727; Characteristic ^{13}C N (pyridine-d_5): δ = 173.7 (1-C), 171.7, 170.8, 170.0 (OAc), 103.8 (11-C 93.8 (1'-C); ^1H NMR (300 MHz, pyridine-d_5): δ = 2.0(s, 3H, OAc), 2.05(3H, OAc), 2.1(s, 3H, OAc), 2.8(d, d, J = 12Hz, J = 4.5Hz, 1H, 12-H eq 3.2(s, 3H, CH_3-acetale), 3.6(s, 3H, CH_3-ester), 3.7(m, 1H, 15-H), 3.95(1H, 13-H), 4.25(m, 2H, 5'-H, 9-H), 5.1(pseudo s, 1H, 1'-H), 5.55(m, 3 3'-H, 4'-H, 7-H).

3',4',7-Tri-O-acetyl-2,3,4,5-tetrahydro-seco-elaiophylin methyl ester (3c

0.45 g (0.67 mmol) of **2c** are dissolved in 10 ml of ethyl acetate a hydrogenated using 100 mg of 10% palladium/carbon (Riedel-de-Haen) normal pressure and room temp. until the calculated amount of hydrogen h

been consumed. After filtering off the catalyst and stripping off the solvent, the residue is crystallized from diisopropyl ether/n-pentane, yield: 0.36 g (79%); m.p. 112-113°C; Analysis for $C_{34}H_{58}O_{13}$ (674.8): calcd C, 60.5; H, 8.6; found C, 60.3; H, 8.6; Characteristic ^{13}C NMR (pyridine-d_5): δ = 173.8 (1-C), 170.1, 170.6, 170.8 (OAc), 100.0 (11-C), 93.8 (1'-C); ^1H NMR (300 MHz, pyridine-d_5): δ = 2.0(s, 3H, OAc), 2.05(s, 3H, OAc), 2.1(s, 3H, OAc), 2.8(d, d, J = 12Hz, J = 4.5Hz, 12-Heq), 3.65(s, 3H, CH_3-ester), 4.2(m, 1H, 15-H), 4.25(m, 1H, 5'-H), 4.4(m, 1H, 13-H), 4.55(m, 1H, 9-H), 5.45(pseudo d, 2H, 7-H, 1'-H), 5.55(pseudo s, 1H, 4'-H), 5.6(m, 1H, 3'-H).

7,11-Anhydro-seco-elaiophylin methyl ester 4a and 4b

0.95 g (1.70 mmol) of **2a** are dissolved at 20°C in 10 ml of anhydrous methanol and 30 mg of $FeCl_3$ are added. After 10 min, the mixture is concentrated and chromatographed on 50 g of silica gel using ethyl acetate/hexane (2:1). The C-11 epimeric products **4b** and **4b** are smoothly separated in each case and are isolated as colourless solids after drying in a high vacuum.

4a: Yield: 0.44 g (49%); R_f value: 0.30 (on silica gel using ethyl acetate; $[\alpha]_D^{20}$ -134° (c = 1, CH_3OH); Analysis for $C_{28}H_{46}O_9$: calcd C, 63.8; H, 8.8; found C, 63.6; H 8.7; IR (KBr) 1715 (C=O), 1640, 1620 cm^{-1} (C=C); FAB MS (NaCl matrix) cluster ion $(M+Na)^+$ m/e = 549; ^1H-NMR (300 MHz, pyridine-d_5): δ = 1.6(d, 3H, J = 6.5 Hz, 6'-H), 3.8-4.3(m, 5H, 4'-H, 5'-H, 9-H, 13-H, 15-H), 3.7(s, 3H, CH_3-ester), 4.6(m, 1H, 3'-H), 5.35(pseudo s, 1H, 1'-H), 6.15(d, 1H, J = 14.8 Hz, 2-H), 6.3(d, d, 1H, J = 10.1 Hz, J = 14 Hz, 4-H), 6.65(d, d, 1H, J = 14 Hz, J = 6.7 Hz, 5-H), 7.65(d, d, 1H, J = 14.8 Hz, J = 10.1 Hz, 3-H).

4b: Yield: 0.38 g (42%); R_f value: 0.16 (on silica gel using ethyl acetate; $[\alpha]_D^{20}$ -58.2° (c= 1, CH_3OH); Analysis for $C_{28}H_{46}O_9$ (526.66): calcd C, 63.8; H, 8.8; found C, 63.6; H, 8.8; IR (KBr) 1715 (c = 0), 1640; FAB MS (NaCl martix) cluster ion $(M+Na)^+$ m/e = 549; ^1H NMR (300 MHz, pyridine-d_5): δ = 1.7(d, 3H, J = 6.5 Hz, 6'-H), 3.5-3.65(4H), 3.7-4.2(m, 4H), 4.6(m, 1H, 3'-H), 5.3(pseudo s, 1H, 1'-H), 6.15(d, 1H, J = 14.8 Hz, 2-H), 6.45(m, 2H, 4-H, 5-H), 7.65(d,d, 1H, J = 14.8 Hz, J = 10.2 Hz).

7,11-Anhydro-2,3,4,5-tetrahydro-seco-elaiophylin methyl ester 5a and 5b

1.25 g (2.23 mmol) of **2a** are dissolved in 50 ml of anhydrous methanol and hydrogenated using 300 mg of 10% palladium/carbon (Merck) at room temp. and normal pressure until the calculated amount of hydrogen has been taken up. The reaction solution is concentrated and the residue is chromatographed on 200 g of silica gel using ethyl acetate/hexane (2:1). The stereoisomeric products **5a** and **5b** are smoothly separated in this case and obtained as colourless oils in a total yield of 82%. **5a**: Yield: 0.55 g (47%); R_f value: 0.30 (on silica gel using CH_2Cl_2/CH_3OH (15:1); $[\alpha]_D^{20}$ -119° (c = 1, CH_3OH);Analysis for $C_{28}H_{50}O_9$ (530.69): calcd C, 63.3; H, 9.5; found C, 63.0; H, 9.4; IR (CH_2Cl_2) 1720 cm^{-1} (methyl ester); FAB MS (NaCl matrix) cluster ion $(M+Na)^+$ m/e = 553; Characteristic ^{13}C NMR (pyridine-d_5): δ = 173.9 (1-C), 100.7 (11-C), 94.5 (1'-C), 51.2 (ester-CH_3); ^1H NMR (300 MHz, pyridine-d_5): δ = 0.8(d, 3H, J = 6 Hz, 21-H), 0.95(t, 3H, J = 6 Hz, 18-H), 1.2(d, 3H, 17-H), 1.4(m, 3H), 1.52(d, 3H, J = 6.5 Hz, 6'-H), 1.55-2.3(m), 2.5(pseudo s, 1H, 2'-Hax.), 3.6-3.7(pseudo s, 2H, 15-H, CH_3O), 3.75(pseudo d, 1H, 9-H), 4.05(m, 2H, 4'-H, 13-H), 4.2(m, 1H, 7-H), 4.25(m, 1H, 5'-H), 4.45(m, 1H, 3'-H), 5.3(pseudo s, 1H, 1'-H).

5b: Yield: 0.41 g (35%); Rf value: 0.19 (on silica gel wi CH_2Cl_2/CH_3OH (15:1); $[\alpha]_D^{20}$ -87° (c = 1, CH_3OH); Analysis for $C_{28}H_{50}$ (530.69): calcd C, 63.3; H, 9.5; found C, 63.0; H 9.6; IR (CH_2Cl_2) 17 cm^{-1} (methyl ester); FAB MS (NaCl matrix) cluster ion $(M+Na)^+$ m/e = 55 Characteristic ^{13}C NMR (pyridine-d_5): δ = 173.8 (1-C), 102.0 (11-C), 94 (1'-C), 51.2 (ester-CH_3); ^1H NMR (300 MHz, pyridine-d5): δ = 0.8(d, 3 J = 6Hz, 21-H), 1.05(t, 3H, J = 6 Hz, 18-H), 3.35(pseudo d, 1H, 9'-H 3.6(s, 3-H, CH_3O), 3.9-4.4(m, 5H), 4.5(m, 1H, 3'-H), 5.4(pseudo s, 1 1'-H).

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