Synthesis of fully functionalized intermediates for the bottom half of the 4-acyloxyethyl milbemycin antibiotics (1)

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Three fully functionalized bottom half synthons for the preparation of the 4-acyloxyethyl milbemycin antibiotics, e.g., milbemycins α9, α10, and F, have been synthesized in only seven steps and reasonable overall yield by an application of our general approach. Either the Δ3 (unisomerized) system or the more common Δ2 (isomerized) system can be prepared by this route.

Résumé – Synthèse des intermédiaires entièrement fonctionnalisés correspondant à la moitié sud des antibiotiques du type 4-acyloxyethyl milbemycine. Trois synthons fonctionnalisés de la moitié sud pour la préparation des antibiotiques de la série 4-acyloxyethyl-milbemycine, c'est-à-dire les milbemycines α9, α10, et F, ont été synthétisés en seulement sept étapes avec un rendement global raisonnable par application de notre approche générale. Le système Δ3 (non isomérisé) ou le système Δ2, plus commun (isomérisé) peuvent être préparé par ce chemin.

reduction / debenzylation / isomerization / milbemycins

réduction / débenzylation / isomérisation / milbemycines

Introduction

The avermectins and milbemycins are naturally occurring antibiotics derived from Streptomyces avermitilis and Streptomyces hygroscopicus subsp. aureolacrimosus, respectively (2). The main difference between the two classes in the presence of the α-L-oleandrosyl-α-L-oleandrosyl unit at C-13 in the avermectins and its lack in the milbemycins. Several derivatives of these natural compounds have found great use in the treatment of parasitic diseases in both animals and humans. For example, 22,23-dihydroivermectin B1a, also called ivermectin, 1, is currently used as both a treatment for onchocerciasis (river blindness) (3a) and as an antiparasitic agent for livestock (3a), while several milbemycin derivatives are used as animal antiparasitic agents (3bc). Therefore, the potential medicinal significance of these compounds is high and has prompted a great deal of synthetic activity, culminating in several total or partial syntheses (4). However, nearly all of this synthetic activity has been directed at the less functionalized avermectin or milbemycin derivatives which have a methyl group at C-4. To date, very little work has been reported on synthetic approaches to the natu-

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ral products having a [(2-pyrroloyl)oxy]methyl at C-4, namely milbemycin α, α₁₀, and F, 2abc, respectively, which differ only in the alkyl group at C-25 (5). We now wish to report an application of our general synthetic scheme (6) for the preparation of synthons for the bottom half of these molecules which permits the rapid construction of fully functionalized intermediates for the 4-acyloyloxy methyl compounds in only a few steps from readily available materials.

Results and discussion

Our synthetic route to highly functionalized intermediates for the bottom half of the avermectins and milbemycins involves the novel cycladdition of the readily available 3,4-bis(benzyloxy)furan 3 and 2-(trimethylsilyl)ethyl coumalate 4 to give the endo and exo adducts 5n and 5x in 88% isolated yield (after careful column chromatography on silica gel) in a ratio of 53:47 (6a). It is interesting to note that in this reaction the aromaticity of two non-benzenoid aromatic rings is lost in a mild thermal (65°C) process (6b). The endo ester 5n is converted to the alcohol 6 in two steps: fluoride ion-promoted deprotection of the ester (86%) and samarium triiodide-mediated reduction of the derived mixed anhydride (71%) (6b). In order to prepare the 4-acyloyloxy methyl bottom-half intermediates, the hydroxymethyl group in 6 must be preserved rather than reduced, as in our earlier sequence (6a). Benzoylation of 6 using silver oxide as the base afforded the tris(benzyloxy) lactone 7 in 86% yield. Opening of the lactone 7 under basic conditions by a slight modification of our procedure in the methyl series (6a) and subsequent methylation with diazomethane furnished the β, γ-unsaturated ester 8 in 64% yield. It is interesting to point out that again in this series with a dihydrofuran ring (having three \(sp^2\)-hybridized atoms) fused to the cyclohexene ring, we see no evidence of movement of the double bond into conjugation with the ester and the \(\Delta^3\) olefin (rather than the \(\Delta^2\) olefin) is the major product. Inversion of the stereochemistry of the alcohol at C-5 was accomplished by Swern oxidation using trifluoroacetic anhydride and DMSO followed by immediate reduction of the crude enone 9 with sodium borohydride in methanol in the presence of cerium trichloride (Luche method) (7). In this case, a 4:3:1 mixture of the desired inverted 5,5'-diol 10 and the starting 5α-alcohol 8 is produced, with the alcohol 10 being isolated in 65% yield (76% based on unrecovered starting material). As in the 4-methyl series, the inverted stereochemistry was inferred from the difference in the coupling constant between the hydrogens at C-5 and C-6, \(J_{5,6}\), which is 12.4 Hz in the 5α-alcohol 8 and only 3.3 Hz in the 3,3'-alcohol 10.

All that remained to reach our goal was the selective removal of the three benzyloxy groups. Even though all three protecting groups are the same, we have achieved some success in their selective removal using transfer hydrogenation. Treatment of the tris(benzyloxy) hydroxy ester 10 with 10% palladium on carbon using cyclohexane-1,4-diene as the hydrogen source gave a readily separa-
mixture of the bis(benzyloxy) hydroxy ester ketone 11 and the mono(benzyloxy) dihydroxy keto ester 12 in isolated yields of 19% and 26% after chromatography, along with a small amount of recovered starting material. As in the 4-methyl series, cyclohexa-1,4-diene does not remove the tertiary benzyl ether under these conditions. The structures were determined primarily by analysis of the high field proton NMR's of 11 and 12 as well as that of the acetate of 11, compound 13. Com- pounds such as 11 and especially 13 may serve as useful intermediates for construction of the 4-acyloxy methylmilbemycins since they are fully functionalized and protected so that further reactions, e.g., addition to the carbonyl or transesterification might be possible. The diol 12 is also potentially useful but would probably require further protection of its hydroxyls (perhaps as a cyclic acetonide or bis silyl ether) before additions to C-1 or C-8. It is quite interesting that in this system, we see isomerization of the double bond into conjugation with the ester and isolate predominantly the \( \Delta^2 \) isomers under these conditions, whereas in the 4-methyl series only the unisomerized \( \Delta^1 \) isomers are obtained (6a). Finally, to show that the system is stable to conditions necessary for complete removal of all the benzyl protecting groups, we have converted 10 into the unisomerized keto triol 14 by transfer hydrogenation using 20% formic acid in methanol over 10% palladium on carbon. This reaction gives quite variable results and depends crucially on the sample and age of the cata-
lyst used. However, we can consistently obtain yields of 30-40% and have on occasion obtained yields as high as 60%. The structure of the product was inferred from the high field proton NMR spectra of 14 and its mono(t-
butyldimethylsilyl) ether 15 and the similarity of these spectra to those of the 4-methyl compound (6a).

Thus we have shown that the readily available starting materials 3 and 4 can be converted into three potentially useful bottom half synthons 11, 12, and 14 by a very direct route in only seven steps. Further reactions in this series are currently underway.

**Experimental**

**General procedures**

\( ^1 \)H NMR spectra were recorded at 500 MHz on a Bruker WM-500 spectrometer with tetrabutylmethane as an internal standard. \( ^{13} \)C NMR spectra were recorded at 125 MHz or 90 MHz on a Bruker WM-500 or a Bruker AM-360 spectrometer, respectively, with deuteriochloroform as an internal standard. IR spectra were recorded on a Perkin-Elmer T10B spectrometer. Mass spectra were taken on an AEI MS-902 mass spectrometer. Analytical thin layer chromato-

graphy (TLC) was performed on precoated silica gel F\( _{254} \) plates and were visualized with iodine or phospho-
molybdcic acid oxidation. Preparative separations were carried out using flash silica gel. All solvents were dried and distilled according to standard procedures. The alcohol 6 was prepared as described in reference 6a.

\( \text{3a,4,7,7a-Tetrahydro-8-[benzyloxy)methyl]-3,3a-dibenzy-
loxy-4,7-etheno-5H-furo[2,3-c]pyran-5-one, 7} \)

A suspension of silver oxide (300 mg), the alcohol 6 (100 mg, 0.24 mmol), and benzyl bromide (346 \( \mu \)L, 2.9 mmol) in freshly distilled dimethylformamide (DMF, 2.0 mL) were stirred at 70°C for 60 min. After cooling, the reaction so-
lution was decanted from the salts and after removal of the solvent in vacuo, the residue was purified by column chromo-

tography on silica gel using dichloromethane as eluent to provide 105 mg of the benzylated product 7 (86%).

500 MHz \( ^1 \)H NMR (CD\(_2\)Cl\(_2\)): \( \delta 6.73 (2H, d, J = 7.5 \text{ Hz}), 7.00-

7.23 (13H, m), 5.77 (1H, dd, J = 6.7, 1.8 Hz), 5.60 (1H, s), 4.82 (1H, dd, J = 4.7, 2.3 Hz), 4.61 (1H, d, J = 4.7 Hz), 4.59 (2H, ABq, J = 11.8 Hz), 4.31 (2H, s), 4.18 (2H, ABq, J = 11.9 Hz), 4.16 (2H, ABq, J = 11.9 Hz), 4.02 (1H, d, J = 6.7 Hz), 3.73 (2H, ABq of d, J = 13.9, 1.7 Hz). 500 MHz \( ^{13} \)C NMR (CD\(_2\)Cl\(_2\)): \( \delta 76.6-73.2 (15 \text{ H}), 62.0 (1H, dd), 6.01 (1H, s), 5.23 (1H, dd), 4.79 (1H, d), 4.70 (2H, ABq), 4.65 (2H, s), 4.48 (2H, ABq), 4.09 (2H, ABq of d), 3.89 (1H, d). Couplings same as above.

125 MHz \( ^{13} \)C NMR (CD\(_2\)Cl\(_2\)): \( \delta 170.3, 141.3, 139.4, 137.7, 137.6, 136.0, 128.5, 128.5, 128.3, 128.1, 129.7, 127.9, 127.5, 127.4, 124.9, 89.2, 79.8, 74.6, 72.6, 72.4, 68.8, 67.2, 47.2.

IR (CHCl\(_3\)): \( \delta 000-3-100, 2860, 1765, 1450, 1350, 1290, 1230, 1180, 1050, 900 \text{ cm}^{-1}\).

Mass spectrum (m/e): \( 496 (m^+), 280, 108, 97, 91 (base). \)

\( \text{Methyl 3a,4,7,7a-tetrahydro-7-hydroxy-6-benzyloxy-
methyl-3,3a-dibenzyloxybenzofuran-4-carboxylate, 8} \)

To a solution of lactone 7 (580 mg, 1.169 mmol) in the mixed solvent system 3:3:4 tetrahydrofuran (THF)-ethanol-water (9 mL: 9 mL: 12 mL) was added aqueous potassium hydroxide (2.92 mmol). The solution was heated to 70°C for 20-30 min, with monitoring by TLC. As soon as TLC showed complete consumption of starting material, the reaction was quenched by addition of water (30 mL) followed by acidification with dilute HCl. The crude reaction mixture was extracted with ethyl acetate (2 x 30 mL) and the combined organic layers dried over Na\(_2\)SO\(_4\). The solvent was removed in vacuo, the crude acid diluted with diethyl ether (5 mL) and the solution cooled to 0°C. A solution of diazomethane in ether was added until TLC showed complete esterification. Removal of the solvent in vacuo and chromatography on silica gel, eluting with dichloromethane and 95:5 dichloromethane-acetone, afforded 395 mg of the tribenzyl hydroxy ester 8 (64%).

500 MHz \( ^1 \)H NMR (CD\(_2\)Cl\(_2\)): \( \delta 7.00-7.30 (15H, m), 5.88 (1H, s), 5.84 (1H, d, J = 12.4 Hz), 5.78 (1H, bd, J = 7.1 Hz), 5.24 (1H, s, OH), 4.61 (1H, d, J = 12.6 Hz), 4.53 (2H, s), 4.35 (1H, d, J = 7.1 Hz), 4.26 (2H, ABq, J = 11.7 Hz), 4.18 (2H, s), 4.10 (2H, ABq of d, J = 13.7, 1.5 Hz), 3.19 (3H, s).

90 MHz \( ^{13} \)C NMR (CD\(_2\)Cl\(_2\)): \( \delta 175.0, 144.3, 138.8, 138.2, 137.6, 136.4, 128.7, 128.6, 128.4, 128.6, 128.0, 127.9, 127.8, 127.7, 127.4, 127.0, 120.2, 88.1, 85.7, 72.6, 72.2, 71.2, 66.5, 66.5, 53.2, 46.7.

IR (CHCl\(_3\)): \( \delta 390, 300, 2960, 2860, 1710, 1495, 1450, 1 1430, 1270, 1090, 1020 \text{ cm}^{-1}\).

Mass spectrum (m/e): \( 328 (M^+), 402, 296, 280, 181, 91 (base). \)

\( \text{Methyl 3a,4,7,7a-tetrahydro-7-hydroxy-6-benzyloxy-
methyl-3,3a-dibenzyloxybenzofuran-4-carboxylate, 10} \)

To a solution of dimethyl sulfoxide (DMSO, freshly dis-
tilled from calcium hydride) (40 \( \mu \)L, 0.57 mmol) in dry dichloromethane (1.5 mL) was added trifluoroacetic anhy-
dride (87 \( \mu \)L, 0.63 mmol, freshly distilled) at −78°C under a nitrogen atmosphere. This solution was stirred for 15 min (or until a white suspension was observed). To this solution was added a solution of the alcohol 8 (100 mg, 0.189 mmol) in dichloromethane (1.5 mL) dropwise at −78°C. The re-
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sulting solution was stirred at −78°C for 30 min followed by addition of triethylamine (200 μL) and warming until the cloudiness of the mixture just disappeared. The reaction was immediately quenched by pipetting into excess dichloromethane (20 mL). This solution was washed with dilute aqueous HCl, half-saturated aqueous sodium bicarbonate and water followed by drying over Na2SO4. After removal of the solvent in vacuo, and pulling a high vacuum for a few minutes, the crude enone 9, was submitted to reduction without further purification.

To a solution of crude enone 9 and cerium trichloride heptahydrate (73 mg) in 7 mL of methanol cooled to 0°C was added sodium borohydride (5 mg, 0.21 mmol) in portions over 10 min. After TLC showed complete reduction, the reaction was quenched at 0°C with saturated aqueous ammonium chloride. The methanol was then removed in vacuo with warming, the residue diluted with a minimum amount of water, and extracted several times with dichloromethane. After drying over Na2SO4, the solvent was removed in vacuo and the residue chromatographed on silica gel, eluting with 95:5 dichloromethane-acetone, to give first recovered ester 8 (15 mg, 15%) and then the inverted tris(benziloxyl)hydroxyester 10 (55 mg, 65% yield, 76.3% based on unrecovered starting material).

12: 500 MHz 1H NMR (CDCl3): δ 7.30-7.39 (9H, m), 6.96 (1H, d, J = 2.1 Hz), 4.60 (2H, s), 4.32 (1H, d, J = 2.4 Hz), 4.26 (1H, d, J = 17.6 Hz), 4.09 (1H, d, J = 17.6 Hz), 4.02 (1H, dd, J = 9.4, 2.4 Hz), 3.81 (1H, d, J = 9.3 Hz, OH), 3.79 (3H, s), 3.67-3.82 (3H, m), 2.98 (1H, m).

Methyl 2,3,3a,4,7,7a-hexahydro-2,7-dihydroxy-6-hydroxyethylmethyl-3-oxobenzofuran-4-carboxylate, 14; 6-(t-butyldimethylsilyl)ether, 15

A mixture of 10% palladium on carbon (4 mg) and the inverted tribenziloxyl hydroxy ester 10 (3.3 mg, 0.006 mmol) in 300 μL of 20% methanolic formic acid (freshly prepared) was stirred at 25°C under a nitrogen atmosphere (until TLC showed major formation of very low Rf spots). The catalyst was filtered and washed several times with hot methanol. After evaporation of the solvent, the residue was chromatographed on silica gel, eluting first with 80:20 dichloromethane-acetone and then with 70:30 dichloromethane-acetone with a trace of acetic acid to afford the desired trihydroxy keto ester 14 (0.7 mg, 43%). This reaction was poorly reproducible, with yields varying from 30-60%, presumably due to differences in the catalyst. The primary t-butyldimethylsilyl ether 15 was prepared by standard means (1 eq. t-butyldimethylsilyl trflate, lutidine, dichloromethane, 25°C) to help in the structure determination.

14: 500 MHz 1H NMR (CDCl3): δ 5.86 (1H, d, J = 4.5 Hz), 4.96 (1H, dd, J = 8.5, 4.1 Hz), 4.88 (1H, t, J = 10.2 Hz, OH), 4.76 (1H, s, OH), 4.56 (1H, d, J = 4.5 Hz), 4.24 (2H, Abq, J = 17 Hz), 3.73 (3H, s), 3.50-3.70 (3H, m), 3.42 (1H, d, J = 8.5 Hz, OH).

A mixture of 10% palladium on carbon (12 mg), cyclohexyl-N,N-diethoxyphosphoric acid (100 μL) and the inverted tribenzoxyl hydroxy ester 10 (10 mg, 0.019 mmol) in 500 μL of 95% ethanol was stirred under a nitrogen atmosphere for 3 d at 25°C. The catalyst was filter and washed several times with hot methanol. After evaporation to dryness, the residue was chromatographed on silica gel, eluting with 80:20 dichloromethane-acetone to give first the isomerized bis(benziloxyl) hydroxy ketone 11 (1.6 mg, 19%) and then the isomerized mono(benziloxyl) dihydroxy ketone 12 (1.7 mg, 26%). To help in structure elucidation, 11 was converted into its 7-acevate 13 (acetic anhydride, pyridine, DMAP) in good yield.

13: 500 MHz 1H NMR (CDCl3): δ 7.27-7.39 (10H, m), 7.09 (1H, d, J = 2.2 Hz), 4.64-4.58 (2H, Abq, J = 11.0 Hz), 4.60 (2H, s), 4.45 (1H, d, J = 2.4 Hz), 4.25 (1H, d, J = 17.4 Hz), 4.09 (1H, dd, J = 9.3, 2.4 Hz), 4.04 (1H, d, J = 17.4 Hz), 3.86 (1H, dd, J = 9.1, 4.8 Hz), 3.76 (3H, s), 3.72 (1H, dd, J = 8.8, 7.0 Hz), 2.93 (1H, m).

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References

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