Bull Soc Chim Fr (1990) 127, 830-834

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

ME Jung* , DB Head

Department of Chemistry and Biochemistry, University of California, Los Angeles, CA 90024 USA

(received June 6 1990, accepted August 16 1990)

Three fully functionalized bottom half synthons for the preparation of the 4-acyloxymethyl milbemycin antibiotics, e.g., milbemycins α_9, α_{10}, and F, have been synthesized in only seven steps and reasonable overall yield by an application of our general approach. Either the Δ^3 (unisomerized) system or the more common Δ^2 (isomerized) system can be prepared by this route.

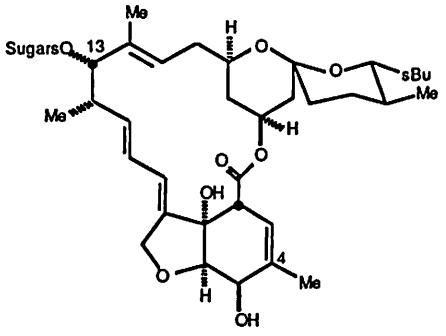
reduction / debenzylation / isomerization / milbemycins

Résumé – Synthèse des intermédiaires entièrement fonctionnalisés correspondant à la moitié sud des antibiotiques du type 4-acyloxyméthyl milbemycine. *Trois synthons fonctionnalisés de la moitié sud pour la préparation des antibiotiques de la série 4-acyloxyméthyl-milbemycine, c'est-à-dire les milbemycines α_9, α_{10}, et F, ont été synthétisés en seulement sept étapes avec un rendement global raisonnable par application de notre approche générale. Le système Δ^3 (non isomérisé) ou le système Δ^2, plus commun (isomérisé) peuvent être préparé par ce chemin.*

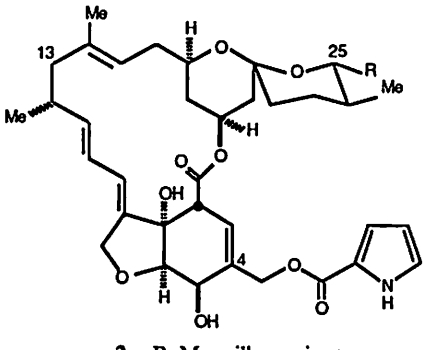
réduction / débenzylation / isomérisation / milbemycines

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-dihydroavermectin B_{1a}, 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-



1 ivermectin



2a R=Me milbemycin α_9
2b R=Et milbemycin α_{10}
2c R=iPr milbemycin F

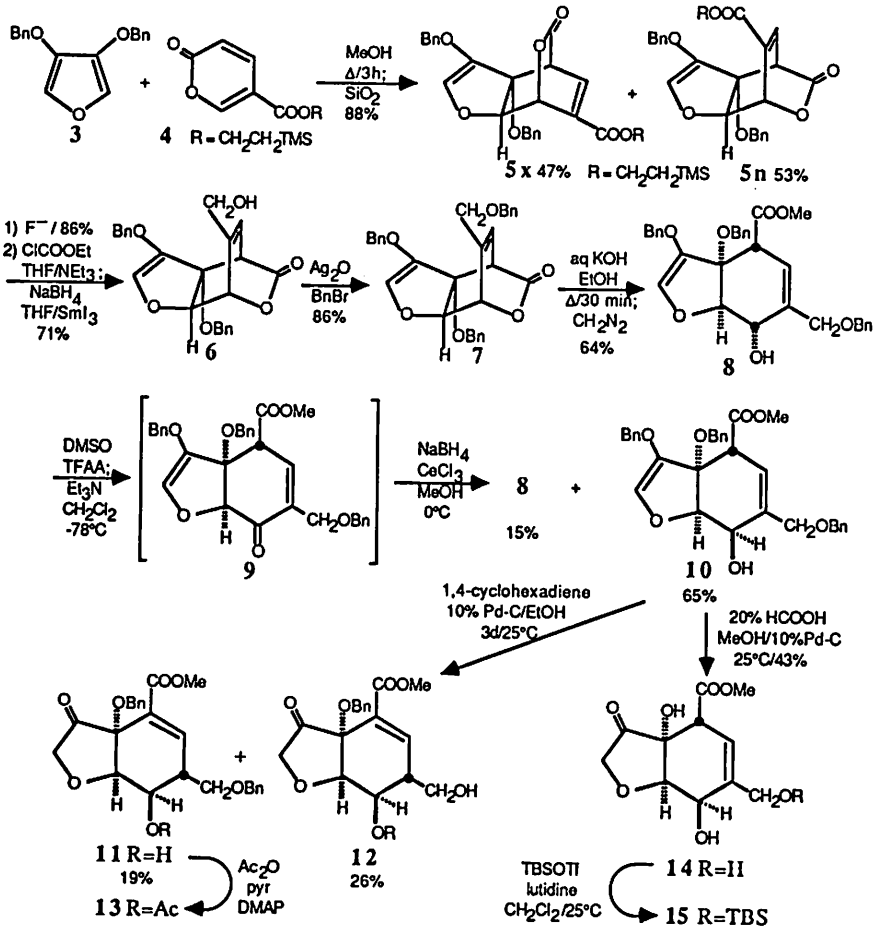
* Correspondence and reprints

ral products having a [(2-pyrroloyl)oxy]methyl at C-4, namely milbemycin α_9, α_{10}, 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-acyloxymethyl 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 cycloaddition 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-acyloxymethyl bottom-half intermediates, the hydroxymethyl group in **6** must be preserved rather than reduced, as in our earlier sequence (6a). Benzylation 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 Δ^3 olefin (rather than the Δ^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 5β-alcohol **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 5.3 Hz in the 5β-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 cyclohexa-1,4-diene as the hydrogen source gave a readily separa-



ble 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**. Compounds such as **11** and especially **13** may serve as useful intermediates for construction of the 4-acyloxymethyl milbemycins 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 predominately the Δ^2 isomers under these conditions, whereas in the 4-methyl series only the unisomerized Δ^3 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 catalyst 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 tetramethylsilane 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 710B spectrometer. Mass spectra were taken on an AEI MS-902 mass spectrometer. Analytical thin layer chromatography (TLC) was performed on precoated silica gel F_{254} plates and were visualized with iodine or phosphomolybdic 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.

3a,4,7,7a-Tetrahydro-8-[benzyloxymethyl]-3,3a-dibenzyloxy-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 μL, 2.9 mmol) in freshly distilled dimethylformamide (DMF, 2.0 mL) were stirred at 70°C for 60 min. After cooling, the reaction solution was decanted from the salts and after removal of the solvent in vacuo, the residue was purified by column chromatography on silica gel using dichloromethane as eluent to provide 105 mg of the benzylated product **7** (86%).

500 MHz ^{1}H NMR (C_6D_6) : δ 7.36 (2H, d, J = 7.5 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 ^{1}H NMR ($CDCl_3$) 7.26-7.32 (15 H), 6.20 (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), 3.98 (1H, d). Couplings same as above.

125 MHz ^{13}C NMR ($CDCl_3$) : δ 170.3, 141.4, 139.4, 137.7, 137.6, 136.0, 128.6, 128.5, 128.3, 128.1, 127.9, 127.7, 127.5, 127.4, 127.3, 124.4, 89.2, 79.8, 74.6, 72.6, 72.4, 68.8, 67.2, 47.2.

IR ($CHCl_3$) : 3 000-3 100, 2 860, 1 765, 1 450, 1 320, 1 290, 1 230, 1 150, 1 080, 990 cm^{-1}.

Mass spectrum (m/e) : 496 (m^+), 280, 108, 107, 91 (base).

Methyl 3a,4,7,7a-tetrahydro-7-hydroxy-6-benzyloxymethyl-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 × 30 mL) and the combined organic layers dried over Na_2SO_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 (C_6D_6) : δ 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 ($CDCl_3$) : δ 175.0, 144.3, 138.8, 138.2, 137.6, 136.4, 128.7, 128.6, 128.44, 128.36, 128.0, 127.9, 127.8, 127.7, 127.4, 127.0, 120.2, 88.1, 85.7, 72.6, 72.2, 71.2, 68.5, 65.4, 53.2, 46.7.

IR ($CHCl_3$) : 3 380, 3 010, 2 960, 2 860, 1 710, 1 495, 1 450, 1 430, 1 350, 1 270, 1 090, 1 020 cm^{-1}.

Mass spectrum (m/e) : 528 (M^+), 402, 296, 280, 181, 91 (base).

Methyl 3a,4,7,7a-tetrahydro-7-hydroxy-6-benzyloxymethyl-3,3a- dibenzyloxybenzofuran-4-carboxylate, **10**

To a solution of dimethyl sulfoxide (DMSO, freshly distilled from calcium hydride) (40 μL, 0.57 mmol) in dry dichloromethane (1.5 mL) was added trifluoroacetic anhydride (87 μL, 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-

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 Na_2SO_4. 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 (8 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 Na_2SO_4, 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(benzyloxy)hydroxy ester **10** (65 mg, 65% yield, 76.5% based on unrecovered starting material).

500 MHz ^{1}H NMR (C_6D_6) : δ 7.33 (2H, d, J = 7.6 Hz), 7.25 (2H, d, J = 7.2 Hz), 7.03-7.20 (13H, m), 5.83 (1H, s), 5.77 (1H, dd, J = 11.1, 5.3 Hz), 5.73 (1H, bd, J = 7.5 Hz), 5.13 (1H, d, J = 5.3 Hz), 4.57 (2H, ABq, J = 12 Hz), 4.16-4.33 (6H, m), 3.96 (1H, 1/2 of ABq, J = 13.1 Hz), 3.25 (s, 3H), 3.13 (1H, d, J = 11.1 Hz, OH).

IR ($CHCl_3$) : 3 520, 3 010, 2 950, 2 920, 2 860, 1 730, 1 495, 1 450, 1 435, 1 345, 1 175, 1 090, 1 060, 1 020, 910 cm^{-1}

MS (m/e) : 528 (M^+), 91 (base).

Methyl 2,3,3a,6,7,7a-hexahydro-7-hydroxy-3-oxo-3a-benzyloxy-6-benzyloxymethylbenzofuran-4-carboxylate, **11** *; 7-acetate,* **13**

Methyl 2,3,3a,6,7,7a-hexahydro-7-hydroxy-6-hydroxymethyl-3-oxo-3a-benzyloxybenzofuran-4-carboxylate, **12**

A mixture of 10% palladium on carbon (12 mg), cyclohexa-1,4-diene (100 μL) and the inverted tribenzyloxy 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 filtered 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(benzyloxy) hydroxy ketone **11** (1.6 mg, 19%) and then the isomerized mono(benzyloxy) dihydroxy ketone **12** (1.7 mg, 26%). To help in structure elucidation, **11** was converted into its 7-acetate **13** (acetic anhydride, pyridine, DMAP) in good yield.

11 : 500 MHz ^{1}H NMR ($CDCl_3$) : δ 7.27-7.38 (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).

13 : 500 MHz ^{1}H NMR ($CDCl_3$) : δ 7.26-7.55 (11H, m), 5.44 (1H, dd, J = 9.9, 2.3 Hz), 4.62 (2H, s), 4.59 (1H, d, J = 2.1 Hz), 4.56 (1H, d, J = 12.0 Hz), 4.49 (1H, d, J = 12.0 Hz), 4.24 (1H, d, J = 17.3 Hz), 4.02 (1H, d, J = 17.3 Hz), 3.77 (3H, s), 3.69 (1H, dd, J = 9.2, 3.5 Hz), 3.58 (1H, dd, J = 9.3, 5.1 Hz), 3.07 (1H, m), 2.08 (3H, s).

12 : 500 MHz ^{1}H NMR ($CDCl_3$) : δ 7.30-7.39 (5H, 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-3a,7-dihydroxy-6-hydroxymethyl-3-oxobenzofuran-4-carboxylate, **14** *; 6-(t-butyldimethylsilyl)ether,* **15**

A mixture of 10% palladium on carbon (4 mg) and the inverted tribenzyloxy 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 R_f 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 triflate, lutidine, dichloromethane, 25°C) to help in the structure determination.

14 : 500 MHz ^{1}H NMR ($CDCl_3$) : 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).

15 : 500 MHz ^{1}H NMR ($CDCl_3$) : δ 5.81 (1H, d, J = 4.5 Hz), 4.83 (1H, dd, J = 8.6, 3.7 Hz), 4.79 (1H, s, OH), 4.41 (1H, d, J = 4.5 Hz), 4.20 (2H, ABq, J = 12.9 Hz), 3.7 (3H, s), 3.60-3.75 (2H, m), 3.41 (1H, d, J = 8.7 Hz), 1.54 (9H, s), 0.05 (3H, s), 0.04 (3H, s).

Acknowledgement

We thank the National Institutes of Health (GM-31349) for generous financial support and Ms Fabienne Berchier for the preparation of alcohol **6**.

References

(1) This manuscript is dedicated to the memory of Jacqueline Ficini, my good friend and mentor.

(2) Davies HG, Green RH *Nat Prod Rep* (1986) **3**, 87

(3) a) Baker R, Swain CJ *Chem Brit* (1989) 692
b) Beddall NE, Howes PD, Ramsay MVJ, Roberts SM, Slawin AMZ, Sutherland DR, Tiley EP, Williams DJ *Tetrahedron Lett* (1988) **29**, 2595 and references therein
c) Asato G, France DJ *Eur Pat Appl EP 259, 779; Chem Abstr* (1988) **109**, 190134m; Asato G, Tamura SY *Eur Pat Appl EP 280, 927-8; Chem Abstr* (1989) **110**, 94860v, 94861w

(4) a) White JD, Bolton GL *J Am Chem Soc* (1990) **112**, 1626 and references therein
b) Danishefsky SJ, Armistead DM, Wincott FE, Selnick HG, Hungate R *Ibid* (1989) **111**, 2967 and references therein

(5) a) Mrozik H *US 4, 457, 920; Eur Pat Appl EP 74, 758; Chem Abstr* (1984) **101**, 211645f; (1983) **99**, 71130x
b) Fraser-Reid B, Barchi J Jr, Faghih R *J Org Chem* (1988) **53**, 923

(6) a) Jung ME, Usui Y, Vu CT *Tetrahedron Lett* (1987) **28**, 5977
b) Jung ME, Street LJ, Usui Y *J Am Chem Soc* (1986) **108**, 6810
c) For a complete discussion, see : Jung ME, "Problem Solving in Organic Synthesis : The False Steps, Failed Pathways, and Ultimately Successful Route to the Bottom Half of Ivermectin", in *Strategies and Tactics in Organic Synthesis*, Vol 2, Academic, New York (1989) p 221

(7) a) Luche JL *J Am Chem Soc* (1978) **100**, 2226
b) Gemal AL, Luche JL *Ibid* (1981) **103**, 5454
c) Luche JL, Rodriguez-Hahn L, Crabbé P *J Chem Soc Chem Commun* (1978) 601