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A Biomimetic Approach to the Pyridone Rings of the Acromelic Acids: A Concise Synthesis of Acromelic Acid A and an Approach to Acromelic Acid B.

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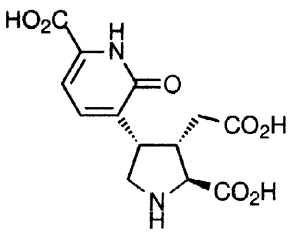
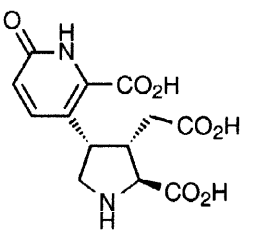
Abstract: *The syntheses of acromelic acid A* **1**, *allo-acromelic acid A* **19** *and an approach towards acromelic acid B* **2** *are described. Palladium (0) catalysed cross-coupling reactions were used to generate C-4 catechol precursors and formation of the pyridone rings was investigated using a biomimetic oxidative cleavage - recyclisation strategy.*

Acromelic acid A **1** and acromelic acid B **2** are members of the kainoid[1] family of non-proteinogenic amino acids, isolated in 1983 from the poisonous Japanese mushroom *Clitocybe acromelalga*.[2,3] The kainoids exhibit potent neuroexcitatory activity in the mammalian central nervous system[4] and the symptoms which they induce closely resemble those seen in cases of Alzheimer's disease, Huntington's chorea, epilepsy and various other neurodegenerative disorders.[5] Acromelic acids A **1** and B **2** and analogues of them are therefore in high demand as tools for neuropharmacological research.



Acromelic acid A **1**



Acromelic acid B **2**

Figure 1

We recently reported in preliminary form, concise and efficient syntheses of **1** and *allo*-acromelic acid A **19**.[6] Herein, we wish to report in more detail, the syntheses of **1** and **19** and an approach towards **2**. Our aim was to access **1** and **2** using the kainoid synthesis which we have recently developed[7] and incorporate a biomimetic strategy to form the C-4 pyridone substituents.[8]

The biogeneses of **1** and **2** are thought to involve the condensation of L-glutamic acid with pyridones **3** and **4** respectively (Scheme 1).[2,9] Pyridones **3** and **4** could derive from ammonolysis of the corresponding

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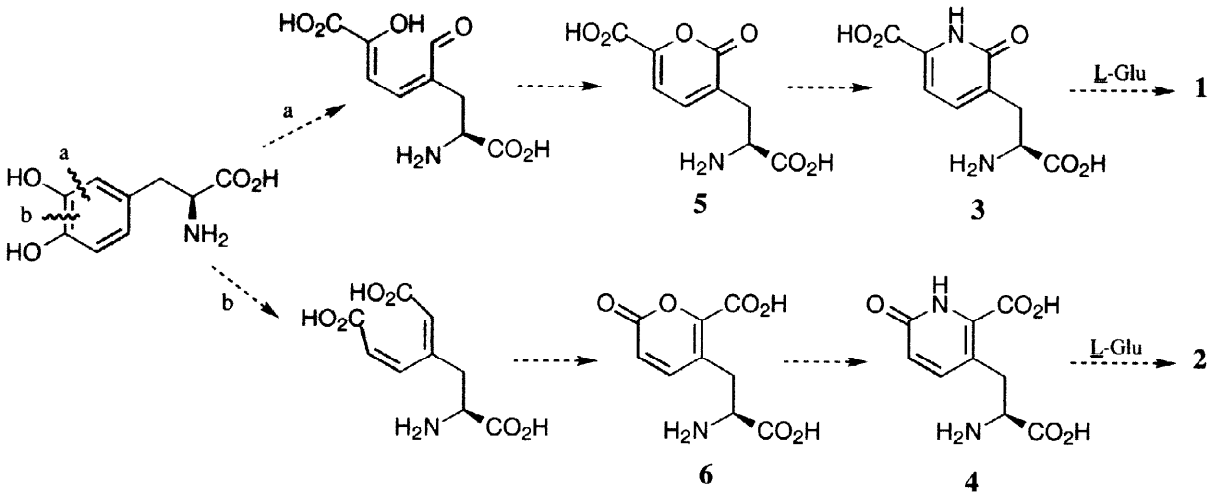
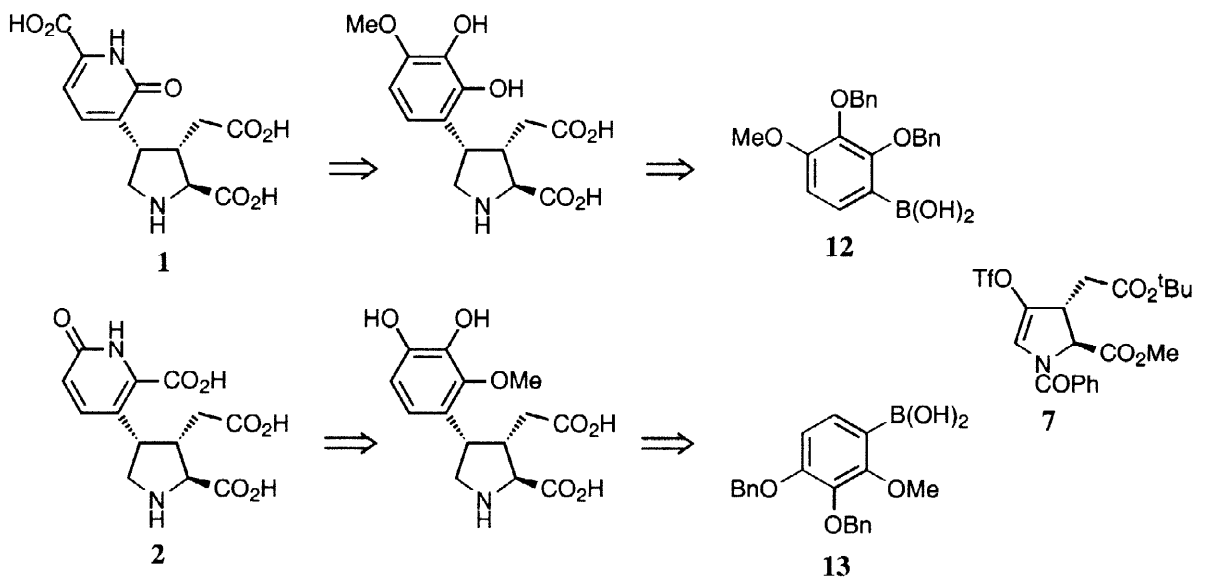
pyrones stizolobinic acid **5** and stizobolic acid **6**. It has been proposed that **5** and **6** in turn, arise from the extra- and intradiol oxidative cleavage of L-DOPA respectively, with subsequent recyclisation and oxidation.



Scheme 1

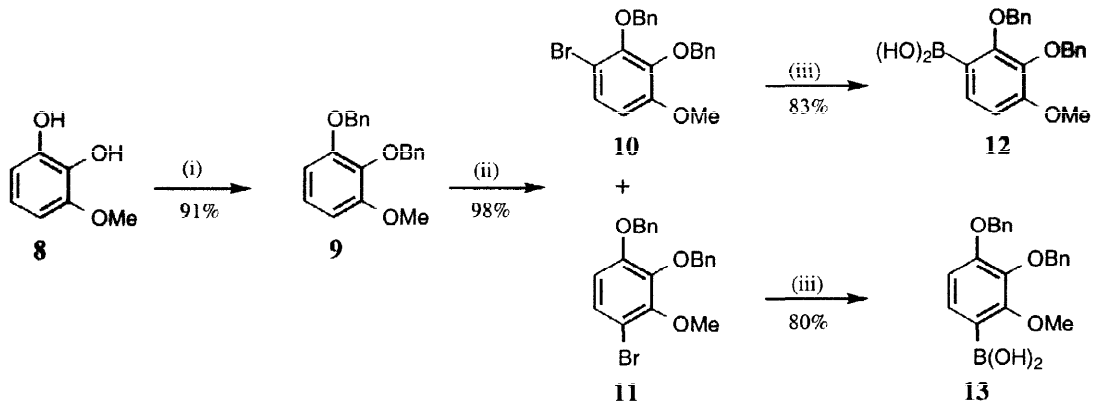
With this in mind, we envisaged that the pyridone substituents of **1** and **2** could be formed from the corresponding pyrones which could themselves be constructed from the oxidative cleavage of appropriate catechols with subsequent recyclisation (Scheme 2). The C-4 catechol substituent would be introduced by the Suzuki cross-coupling reaction[10] of an appropriate boronic acid with vinyl triflate **7** which is readily available in six steps from *trans*-4-hydroxy-L-proline in 34% overall yield.[7b]



Scheme 2

The boronic acids were synthesised from commercially available 3-methoxycatechol **8**. Benzyl ethers were chosen to protect the catechol since these groups could be easily removed by hydrogenation at a later stage (Scheme 3). Treatment of **8** with benzyl bromide and potassium carbonate in dimethylformamide gave **9**

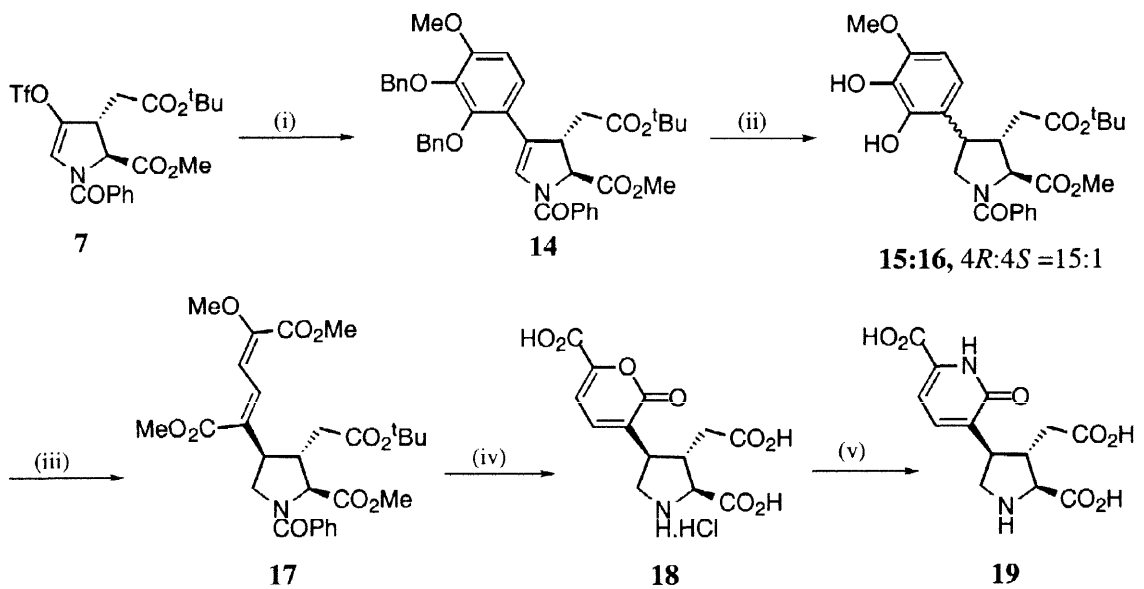
in good yield (91%) and bromination of **9** with N-bromosuccinimide gave the required bromide isomers **10** and **11** in a 1:1 ratio and combined yield of 98%. These two isomers could be readily separated by chromatography and fractional crystallisation. Transmetallation of the bromides with *n*-butyllithium and quenching of the organolithium species with trimethylborate gave boronic acids **12** and **13** after acidic hydrolysis.



Reagents: (i) BnBr, K_2CO_3, DMF; (ii) NBS, CCl_4, RT.; (iii) n-BuLi, THF, -78°C, then $B(OMe)_3$, then sat. NH_4Cl (aq.).

Scheme 3

The Suzuki cross-coupling reaction of vinyl triflate **7** with **12** was then carried out using conditions reported by Wustrow[11] to give enamide **14** (Scheme 4). It was known from our previous work that heterogeneous catalytic hydrogenation of enamides analogous to **14** occurs from the opposite face to the ester at C-2, giving predominantly the wrong stereochemistry at C-4.[7c] Indeed, hydrogenation of **14** over palladium black in ethyl acetate gave a 15:1 mixture of **15** and **16** in favour of the undesired 4*R* isomer **15**.

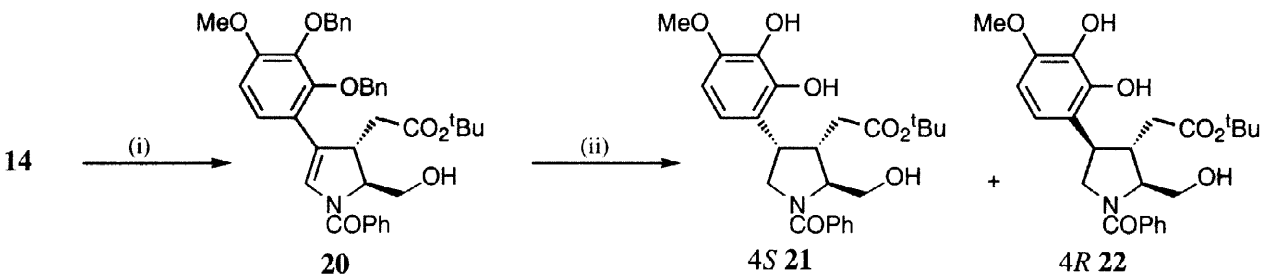


Reagents: (i) **12**, $Pd(PPh_3)_4$, DME, 2M (aq.) Na_2CO_3, LiCl, Δ, 67%; (ii) H_2, Palladium black, EtOAc, RT., quant.; (iii) Ag_2CO_3 on Celite®, CH_2Cl_2, RT., then $Pb(OAc)_4$, MeOH, CH_2Cl_2, 0°C, HPLC, 81%; (iv) conc. HCl, 100°C; (v) NH_3(aq), RT., quant.

Scheme 4

Before controlling the stereochemistry at C-4 we decided to investigate the feasibility of the oxidative cleavage-recyclisation strategy for constructing the pyridone rings. Separation of the C-4 epimeric mixture **15**, **16** was not possible at this stage and so the mixture was treated with Fétizon's reagent[12] (silver carbonate on Celite®) giving intermediate *ortho*-quinones which were oxidatively cleaved using lead tetraacetate and methanol.[13] Purification by preparative HPLC gave the muconate derivative **17** as a single diastereoisomer in good yield. Treatment of **17** with hot concentrated hydrochloric acid induced cyclisation and global deprotection to give pyrone **18** in quantitative yield. Finally, ammonolysis produced *allo*-acromelic acid A **19** in approximately 15% overall yield over 11 steps from *trans*-4-hydroxy-L-proline. The successful synthesis of **19** demonstrated that the biomimetic strategy for constructing the pyridone rings of **1** and **2** was indeed possible. Establishment of the correct stereochemistry at C-4 was now investigated.

Heterogeneous and homogeneous catalytic hydrogenations can be directed by certain substrate functional groups including amines, alcohols and amides.[14] We envisaged that an alcohol substituent at C-2 would guide hydrogenation from the top face of the molecule as required. To this end, chemoselective reduction of the methyl ester of **14** using sodium borohydride gave alcohol **20** in good yield and hydroxyl directed hydrogenation was then attempted (Scheme 5). In previous work[15,7e] synthesising simpler C-4 aryl kainoid analogues, we observed complete stereocontrol in the hydroxyl directed enamide hydrogenation but here we observed a trace of the undesired 4*R* isomer. Hydrogenation of **17** was repeated with different catalysts and solvents in an attempt to improve the selectivity (Table 1). Solvents with low dielectric constants were chosen since these are known to enhance substrate haptophilicity (i.e. the ability of the substrate to coordinate with the catalyst).[14a]



Reagents: (i) $NaBH_4$ (40eq.), MeOH, 78%; (ii) H_2, Catalyst, Solvent (see Table 1).

Scheme 5

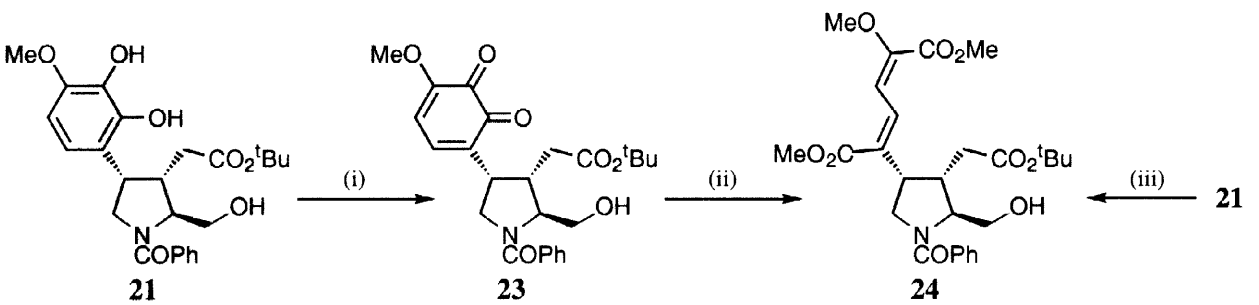
Catalyst	Solvent	H_2 Pressure (atm)	Ratio of 21:22
Palladium black	Ethyl acetate	4	10:1
Palladium black	10:1 Hexane/1,4-dioxane	4	11:1
Palladium black	10:1 Hexane/1,4-dioxane	1.5	8:1
Palladium black	Benzene	4.5	11:1
10% Palladium on C[a]	10:1 Hexane/1,4-dioxane	1	3:1
10% Palladium on C[a]	Ethyl acetate	1	3:1
Raney® nickel	Ethyl acetate	3.5	No reduction observed

a. partial oxidation to the *ortho*-quinone occurred on exposure to air.

Table 1

Total selectivity in the hydrogenation was not achieved, possibly as a result of the catechol competing for available coordination sites on the catalyst, thus allowing partial hydrogenation to occur from the lower face of the molecule. Prolinols **21** and **22** were obtained quantitatively in an 11:1 ratio (in favour of the desired 4*S* isomer **21**) using palladium black in 10:1 v/v hexane/1,4-dioxane.

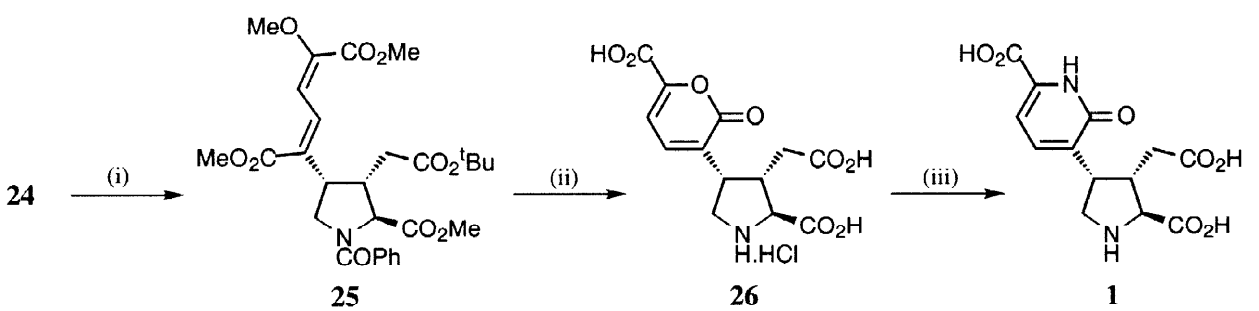
Separation of the C-4 epimers at this stage was not readily achievable and so the 11:1 mixture was carried through until the final step of the synthesis (only the major isomer from each step is shown in Schemes 6 and 7 and reported in the experimental section). As before, catechol **21** was oxidised with Fétizons reagent to the *ortho*-quinone **23** which on treatment with lead tetraacetate and methanol gave muconate derivative **24** (Scheme 6). A faster, one-step oxidative cleavage could also be achieved using two equivalents of lead tetraacetate in methanol at room temperature.



Reagents: (i) Ag_2CO_3 on Celite®, CH_2Cl_2, RT.; (ii) $Pb(OAc)_4$ (1eq.), MeOH, 0°C, 98%, (iii) $Pb(OAc)_4$ (2eq.), MeOH, RT., 95%

Scheme 6

Jones oxidation of **24** and subsequent esterification of the acid with (trimethylsilyl)diazomethane furnished tetraester **25** in 54% yield. Epimerisation of the α-centre was not detected by ^1H NMR (300MHz) (Scheme 7). Heating **25** under reflux with 6M hydrochloric acid gave the desired pyrone **26**. Finally, ammonolysis of the crude pyrones with aqueous ammonia produced acromelic acid A **1** and *allo*-acromelic acid A **19** as an 11:1 mixture in quantitative yield over 2 steps after partial purification with Dowex® 50WX8 ion-exchange chromatography.

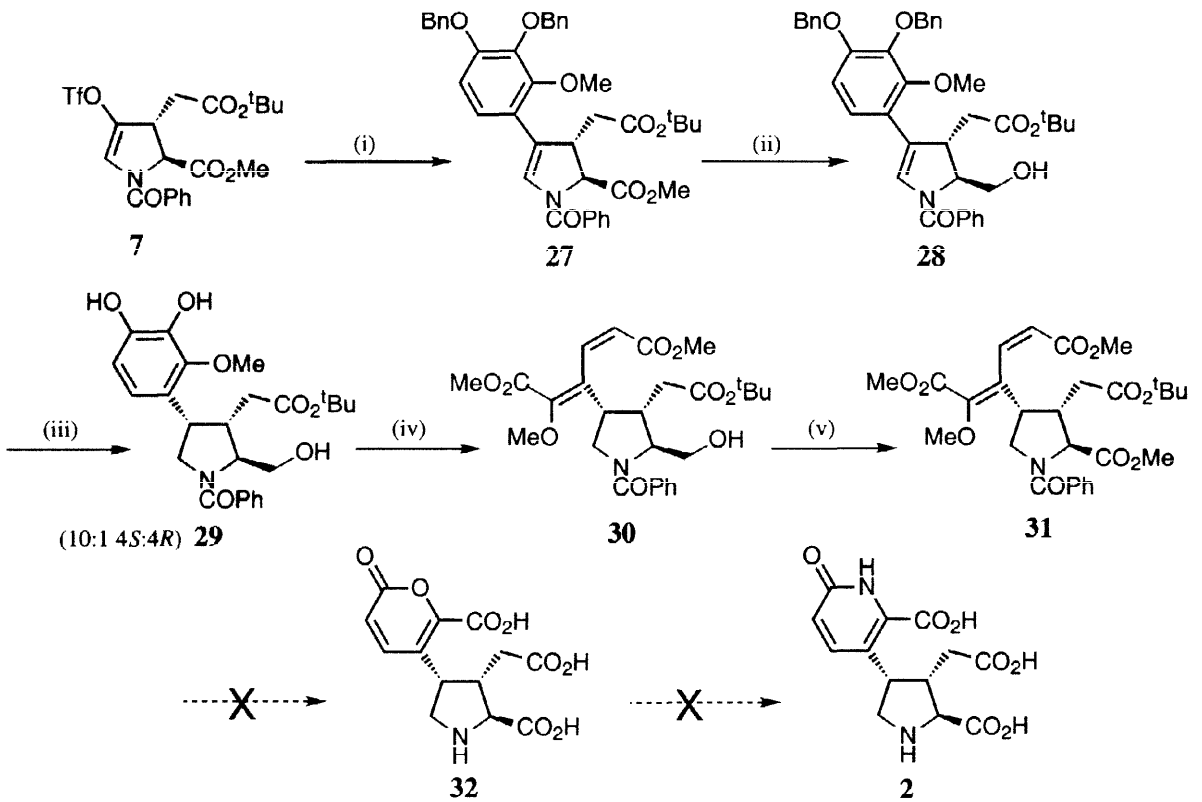


Reagents: (i) CrO_3, conc. H_2SO_4, acetone, H_2O then $TMSCHN_2$, MeOH/PhH, 54%; (ii) 6M HCl (aq.), reflux; (iii) NH_3 (aq.), RT., then Dowex® 50WX8, 100%, then activated charcoal, cellulose chromatography, 60%.

Scheme 7

Purification of the solid by crystallisation was unsuccessful but separation of the C-4 epimers was achieved using cellulose chromatography after filtration through activated charcoal. Acromelic acid A **1** was obtained as a white micro-crystalline solid ($[\alpha]_D^{23}$+27.5 (c 0.28, H_2O), Lit.[2b] $[\alpha]_D$+27.8 (c 0.35, H_2O)) in 9% overall yield in 13 steps from *trans*-4-hydroxy-L-proline.

In a similar fashion, the synthesis of acromelic acid B **2** was attempted. Suzuki cross-coupling of **7** with **13** followed by reduction of the methyl ester of **27** gave alcohol **28** in good yield (Scheme 8). Hydroxyl directed hydrogenation of enamide **28** over palladium black in ethyl acetate quantitatively gave a 10:1 mixture of C-4 epimeric catechols in favour of the correct isomer **29** (only the major isomer from each step is shown in Scheme 8 and reported in the experimental section).



Reagents: (i) **13**, $Pd(PPh_3)_4$, 2M Na_2CO_3(aq.), LiCl, DME, 74%; (ii) $NaBH_4$ (40eq.), MeOH, RT., 74%; (iii) H_2 (1atm.), palladium black, EtOAc, 100%; (iv) $Pb(OAc)_4$ (2eq.), MeOH, RT., 63%; (v) CrO_3, conc. H_2SO_4, H_2O, acetone then CH_2N_2, Et_2O, CH_2Cl_2, 56%.

Scheme 8

Oxidative cleavage of **29** with lead tetraacetate and methanol gave muconate derivative **30** which, after oxidation and esterification, produced tetraester **31**. Treatment of **31** with standard hydrolysis and ammonolysis conditions was studied extensively, but the cyclisations gave complex product mixtures. Although crude ^1H NMR gave a good indication that some of the desired pyrone **32** had formed, it was not possible to isolate a pure sample for full characterisation.

In summary, we have developed a concise synthesis of acromelic acid A **1** in 9% overall yield from *trans*-4-hydroxy-L-proline which is amenable to practice on a multi-gram scale. The pyridone ring was constructed efficiently from a catechol by a biomimetic oxidative cleavage, recyclisation strategy. A similar

approach to generate the pyridone ring of acromelic acid B **2** was not as facile but gave evidence to suggest that the conversion was possible.

Experimental

Melting points were obtained using a Büchi 510 capillary apparatus and are uncorrected.

Specific optical rotations were determined with a Perkin-Elmer 241 automatic polarimeter with a cell of path length 1dm. Concentrations are given in g/100ml.

Infrared spectra were recorded using either a Perkin-Elmer 1750 Fourier transform spectrometer or a Perkin-Elmer Paragon 1000 Fourier transform spectrometer with major absorbances only being quoted. The following abbreviations are used: w, weak; m, medium; s, strong; br, broad.

^{1}H NMR spectra were recorded at 200, 300 and 500MHz using Varian Gemini 200, Bruker AC200, Bruker WH300, Bruker AM500 and Bruker AMX500 instruments. For ^{1}H spectra recorded in $CDCl_3$ or D_2O, chemical shifts are quoted in parts per million and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Coupling constants are quoted to the nearest 0.5Hz.

^{13}C NMR spectra were recorded at 50.3 and 125.8MHz using Varian Gemini 200 and Bruker AM500 or AMX500 instruments using DEPT[16] editing to assist assignment. Chemical shifts are quoted in parts per million and are referenced to $CDCl_3$.

Low resolution mass spectra were recorded on V.G. Micromass ZAB 1F (FAB / CI / DCI) and V.G. Masslab 20-250 (CI / DCI) instruments as appropriate with only molecular ions, fragments from molecular ions and other major peaks being reported. High resolution mass spectra were recorded on a VG ZAB-E instrument.

Flash chromatography was carried out using Sorbsil™ C60 (40-63mm, 230-40 mesh) silica gel as stationary phase. Thin layer chromatography was carried out on aluminium and glass backed plates pre-coated with Merck silica gel 60 F_{254} which were visualised by quenching of u.v. fluorescence or by staining with iodine vapour or 10% w/v ammonium molybdate in 2M sulphuric acid (followed by heat) as appropriate. Cellulose chromatography was carried out on Whatman cellulose powder CF11. Filtration through activated carbon was performed using Darco G60, 100 mesh.

All solvents and reagents were purified by standard techniques reported in Perrin, D. D.; Armarego, W. L. F., *Purification of Laboratory Chemicals*, 3rd edition, Pergamon Press, Oxford, 1988 or used as supplied from commercial sources as appropriate. 40-60 Petroleum ether (40-60 PE) refers to the fraction of light petroleum ether boiling between 40-60°C. Solvents were removed under reduced pressure using a Büchi R110 or R114 Rotavapor fitted with a water or dry ice condenser as necessary.

1,2-Dibenzyloxy-3-methoxybenzene 9

To a stirred solution of 3-methoxycatechol **8** (10.00g, 71mmol) and benzyl bromide (18.7ml, 157mmol) in dimethylformamide (110ml) was added potassium carbonate (21.66g, 157mmol) and the mixture was stirred under an argon atmosphere at room temperature for 24h. The reaction was poured into water (200ml) and the organics extracted with diethyl ether (3 x 300ml). The combined organic extracts were washed with water (2 x 400ml) and saturated brine (400ml), dried ($MgSO_4$), filtered and evaporated to

dryness *in vacuo*. Flash chromatography on silica gel (eluting with 10:1 v/v 40-60 petroleum ether : ethyl acetate) yielded 1,2-dibenzyloxy-3-methoxybenzene **9** (20.70g, 91%) as a colourless oil; R_f 0.35 (9:1 v/v 40-60 PE : EtOAc); υ_{max}/cm^{-1} ($CHCl_3$) 3070w, 2940w, 2253w, 1599s, 1477s, 1106s; δ_H (300MHz; $CDCl_3$) 3.89 (3H, s, Ar-OC<u>H</u>$_3$), 5.10 (2H, s, PhC<u>H</u>$_2$), 5.15 (2H, s, PhC<u>H</u>$_2$), 6.61-6.69 (2H, t, Ar-<u>H</u>), 7.00 (1H, t, Ar-<u>H</u>), 7.27-7.57 (10H, complex, Ph-<u>H</u>); δ_C (50.3MHz; $CDCl_3$) 56.17 (Ar-O<u>C</u>H$_3$), 71.23, 75.18 (2 x Ph<u>C</u>H$_2$), 106.00 (CH$_3$OC<u>C</u>H), 107.70 (PHCH$_2$OC<u>C</u>H), 123.98, 127.67, 128.07, 128.42, 128.76, 128.97 (Ar-<u>C</u>H, Ph-<u>C</u>H), 137.52, 138.15, 138.28, 153.27, 154.37 (Ar-<u>C</u>$_{ipso}$, Ph-<u>C</u>$_{ipso}$); *m/z* (APCI+) 338 (MNH_4^+, 18%), 321 (MH^+, 16), 289 (13), 244 (14), 243 (100), 229 (58), 213 (13), 181 (34), 153 (84), 122 (14).

<u>3,4-Dibenzyloxy-2-methoxy-1-bromobenzene 11 and 2,3-dibenzyloxy-4-methoxy-1-bromo-benzene 10</u>

To a solution of 1,2-dibenzyloxy-3-methoxybenzene **9** (20.45g, 64.0mmol) in carbon tetrachloride (300ml) was added N-bromosuccinimide (25.00g, 141mmol) and the reaction was stirred at room temperature in the dark for 24h. After cooling to 0°C, the mixture was filtered through a silica gel plug (6 x 10cm) and eluted with carbon tetrachloride (400ml). The filtrate was evaporated to dryness *in vacuo* and the residue was purified by flash chromatography on silica gel (eluting with 15:1 40-60 petroleum ether : ethyl acetate) to give 3,4-dibenzyloxy-2-methoxy-1-bromobenzene **11** (12.70g, 50%) as a white crystalline solid; m.p. 71°C; R_f 0.35 (10:1 v/v 40-60 PE : EtOAc); υ_{max}/cm^{-1} ($CHCl_3$) 2941m, 2875w, 1574m, 1498m, 1463s, 1417s, 1372s, 1296s, 1240m, 1075s, 982s; δ_H (300MHz; $CDCl_3$) 3.88 (3H, s, Ar-OC<u>H</u>$_3$), 5.02 (2H, s, PhC<u>H</u>$_2$), 5.03 (2H, s, PhC<u>H</u>$_2$), 6.60 (1H, d, *J* 9Hz, Ar-<u>H</u>), 7.15 (1H, d, *J* 9Hz, Ar-<u>H</u>), 7.25-7.45 (10H, complex, Ph-<u>H</u>); δ_C (50.3MHz; $CDCl_3$) 61.23 (Ar-O<u>C</u>H$_3$), 71.25, 75.64 (2 x Ph<u>C</u>H$_2$), 109.09 (<u>C</u>-Br), 110.87, 127.25, 127.69, 128.34, 128.61, 128.84 (Ar-<u>C</u>H, Ph-<u>C</u>H), 136.84, 137.62, 143.38, 151.85, 153.05 (Ar-<u>C</u>$_{ipso}$, Ph-<u>C</u>$_{ipso}$); *m/z* (APCI+) 423 and 421 (7% and 8%, M+Na$^+$), 410 (12), 409 (12), 401 and 399 (MH^+, 7 and 8), 364 (10), 323 (49), 321 (59), 319 (49), 293 (23), 291 (31), 233 (70), 231 (78), 229 (100), 201 (14), 181 (53), 122 (33) and 2,3-dibenzyloxy-4-methoxy-1-bromobenzene **10** (12.30g, 48%); m.p. 79°C; R_f 0.25 (10:1 v/v 40-60 PE : EtOAc); υ_{max}/cm^{-1} ($CHCl_3$) 2940w, 1576m, 1476s, 1439s, 1368s, 1294s, 1228s, 1094s, 928s; δ_H (300MHz; $CDCl_3$) 3.84 (3H, s, Ar-OC<u>H</u>$_3$), 5.04 (2H, s, PhC<u>H</u>$_2$), 5.07 (2H, s, PhC<u>H</u>$_2$), 6.62 (1H, d, *J* 9Hz, CH$_3$OCC<u>H</u>), 7.24-7.52 (11H, complex, Ar-<u>H</u>, Ph-<u>H</u>); δ_C (50.3MHz; $CDCl_3$) 56.21 (Ar-O<u>C</u>H$_3$), 75.56, 75.72 (2 x Ph<u>C</u>H$_2$), 109.16, 127.36, 128.31, 128.41, 128.57, 128.77, 128.97 (Ar-<u>C</u>H, Ph-<u>C</u>H), 137.12, 137.51, 143.10, 150.48, 153.97 (Ar-<u>C</u>$_{ipso}$, Ph-<u>C</u>$_{ipso}$); *m/z* (Probe CI (NH_3)) 418 and 416 (100% and 100%), 401 and 399 (3 and 3), 246 (17), 198 (6), 108 (35), 91 (7).

<u>2,3-Dibenzyloxy-4-methoxyphenylboronic acid 12</u>

To a solution of 2,3-dibenzyloxy-4-methoxy-1-bromobenzene **10** (5.00g, 12.50mmol) in tetrahydrofuran (100ml) at -78°C under an atmosphere of argon was added *n*-butyllithium (6.6ml of a 2.5M solution in pentane, 16.5mmol) over 5min. Stirring was continued at -78°C for 50min. and then trimethylborate (31.1ml, 27.4mmol) was added and stirring continued for a further 1h. After warming to rt. the mixture was poured onto saturated aqueous ammonium chloride solution (230ml) and the organics were

extracted with diethyl ether (4 x 150ml). The combined organic extracts were washed with saturated brine (200ml), dried ($MgSO_4$), filtered and evaporated to dryness *in vacuo*. Recrystallisation of the residue from 10:1 v/v diethyl ether / 40-60 petroleum ether gave 2,3-dibenzyloxy-4-methoxyphenylboronic acid **12** (3.79g, 83%) as a white solid; m.p. 173-175°C; υ_{max}/cm^{-1} ($CHCl_3$) 3622w, 3500brw, 2960m, 2254s, 1817w, 1795w, 1595s, 1457s, 1438s, 1373s, 1348s, 1290s, 1094s, 978s, 910s; δ_H (200MHz; $CDCl_3$) 3.92 (3H, s, Ar-OC<u>H</u>$_3$), 5.08 (2H, s, PhC<u>H</u>$_2$), 5.19 (2H, s, PhC<u>H</u>$_2$), 6.01 (2H, s, B(O<u>H</u>)$_2$), 6.62 (1H, d, *J* 8Hz, $CH_3OCC\underline{H}$), 7.27-7.62 (11H, complex, Ar-<u>H</u>, Ph-<u>H</u>); δ_C (50.3MHz; $CDCl_3$) 55.99 (Ar-O<u>C</u>H$_3$), 75.57, 76.73 (2 x Ph<u>C</u>H$_2$), 108.25, 117.02, 128.32, 128.60, 128.74, 128.96, 129.18, 131.77 (Ar-<u>C</u>H, Ph-<u>C</u>H), 136.52, 137.58, 140.35, 157.12, 158.27 (Ar-<u>C</u>$_{ipso}$, Ph-<u>C</u>$_{ipso}$); *m/z* (Electrospray, negative ion) 444 (7%), 442 (7), 409 (24), 364 (23), 363 (M-H$^-$, 100), 362 (23).

<u>3,4-Dibenzyloxy-2-methoxyphenylboronic acid 13</u>

To a solution of 3,4-dibenzyloxy-2-methoxy-1-bromobenzene **11** (3.00g, 7.51mmol) in tetrahydrofuran (60ml) at -78°C under an atmosphere of argon was added *n*-butyllithium (4.38ml of a 2.06M solution in pentane, 9.02mmol) over 3min. Stirring was continued at -78°C for 1h and then trimethylborate (17.05ml, 15mmol) was added and stirring continued for a further 1h. After warming to rt. the mixture was poured onto saturated aqueous ammonium chloride solution (100ml) and the organics were extracted with diethyl ether (4 x 100ml). The combined organic extracts were washed with saturated brine (2x300ml), dried ($MgSO_4$), filtered and evaporated to dryness *in vacuo*. Recrystallisation of the residue from 1:1 v/v diethyl ether / 40-60 petroleum ether gave 3,4-dibenzyloxy-2-methoxyphenylboronic acid **13** (2.26g, 80%) as a white solid; m.p. 122-125°C; υ_{max}/cm^{-1} ($CHCl_3$) 3690w, 3621w, 3502brw, 2945w, 1595s, 1522s, 1498s, 1438s, 1348s, 1290s, 1233s, 1186s, 1094s, 978s; δ_H (300MHz; $CDCl_3$) 4.02 (3H, s, Ar-OC<u>H</u>$_3$), 5.03 (2H, s, PhC<u>H</u>$_2$), 5.14 (2H, s, PhC<u>H</u>$_2$), 5.79 (2H, s, B(O<u>H</u>)$_2$), 6.82 (1H, d, *J* 8Hz, BnOCC<u>H</u>), 7.31-7.54 (11H, complex, Ar-<u>H</u>, Ph-<u>H</u>); δ_C (50.3MHz; $CDCl_3$) 61.84 (Ar-O<u>C</u>H$_3$), 70.80, 75.38 (2 x Ph<u>C</u>H$_2$), 109.66, 127.69, 128.28, 128.57, 128.71, 131.63 (Ar-<u>C</u>H, Ph-<u>C</u>H), 136.78, 137.62, 140.54, 156.29, 159.72 (Ar-<u>C</u>$_{ipso}$, Ph-<u>C</u>$_{ipso}$); *m/z* (Electrospray, negative ion) 409 (16%), 407 (10), 364 (19), 363 (M-H$^-$, 100), 362 (23), 353 (12).

<u>(2*S*,3*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2',3'-dibenzyloxy-4'-methoxyphenyl)-[4,5]-dehydropyrrolidine 14</u>

To a vigorously stirred solution of (2*S*,3*R*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonyl methyl-4-trifluoromethanesulphonyloxy-[4,5]-dehydropyrrolidine **7**[7a,b] (1.00g, 1.93mmol) in degassed 1,2-dimethoxyethane (20ml), a solution of 2,3-dibenzyloxy-4-methoxyphenylboronic acid **12** (983mg, 2.70mmol) in 1,2-dimethoxyethane (10ml), 2M aqueous sodium carbonate (10ml), lithium chloride (173mg, 4.08mmol) and tetrakis(triphenylphosphine) palladium (0) (80mg, 69μmol) were added sequentially. The stirred 2-phase system was heated under reflux under an argon atmosphere for 5h. After cooling to room temperature, the solvents were removed *in vacuo* and the residue was partitioned between dichloromethane (100ml) and a mixture of 2M aqueous sodium carbonate (100ml) and concentrated ammonium hydroxide (3ml). The

separated aqueous layer was extracted with dichloromethane (3 x 100ml) and the combined extracts were washed with saturated brine (2 x 300ml), dried ($MgSO_4$), filtered and evaporated to dryness *in vacuo*. Flash chromatography on silica gel (eluting with 15:1 v/v dichloromethane : ethyl acetate) yielded (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2',3'-dibenzyloxy-4'-methoxyphenyl)-[4,5]-dehydropyrrolidine **14** (860mg, 67%) as a pale yellow syrup; R_f 0.45 (9:1 v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{24}$ +32.5 (c 1.18, $CHCl_3$), υ_{max}/cm^{-1} ($CHCl_3$) 1747s, 1724s, 1625s, 1603m, 1447s, 1417s, 1412s, 1392s, 1265s, 1251s, 1047s; δ_H (300MHz; $CDCl_3$) 1.49 (9H, s, $C(CH_3)_3$), 2.28 (1H, *ca.* dd, *J* 9 and 18Hz, $CH_2CO_2Bu^t$), 2.58 (1H, *ca.* dd, *J* 3 and 18Hz, $CH_2CO_2Bu^t$), 3.78-3.90 (7H, complex, CO_2CH_3, $CHCH_2CO_2Bu^t$, Ar-OCH_3), 4.90-5.06 (5H, complex, $CHCO_2CH_3$, 2 x $PhCH_2$), 6.68, 6.89 (2H, ABq, *J* 9Hz, 2 x Ar-CH), 7.13-7.54 (16H, complex, CH=C, Ar-H); δ_C (50.3MHz; $CDCl_3$) 28.00 ($C(CH_3)_3$), 39.47 ($CH_2CO_2Bu^t$), 44.45 (NCHCH), 52.50 (CO_2CH_3), 56.03 (Ar-OCH_3), 63.35 ($CHCO_2CH_3$), 75.01, 75.44 (2 x $PhCH_2$), 81.38 ($C(CH_3)_3$), 107.99, 119.87, 121.54, 122.66, 128.16, 128.27, 128.46, 128.70, 131.00, 134.79, 137.23, 137.56, 142.10 (Ar-CH, Ar-C_{ipso}, NC=C, NC=C), 151.25, 153.60 (Ar-C_{ipso}), 167.46, 170.60, 171.02 (CO_2CH_3, CO_2Bu^t, NC=O); *m/z* (APCI+) 666 (10%), 664 (MH^+, 39), 609 (24), 608 (100), 313 (27), 122 (8); (Found MH^+ 664.2910, $C_{40}H_{42}NO_8$ requires 664.2910).

(2*S*,3*S*,4*R*)-*N*-Benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2',3'-dihydroxy-4'-methoxyphenyl)pyrrolidine 15 and (2*S*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2',3'-dihydroxy-4'-methoxyphenyl)pyrrolidine 16

A solution of (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2',3'-dibenzyloxy-4'-methoxyphenyl)-[4,5]-dehydropyrrolidine **14** (319mg, 0.48mmol) in dry freshly distilled ethyl acetate (20ml) was hydrogenated under a balloon at room temperature in the presence of palladium black (20mg). After 15.5h, fresh catalyst (40mg) was added. After hydrogenation for a further 53h, the reaction mixture was filtered through a pad of $MgSO_4$ (4x5mm). The pad was washed thoroughly with ethyl acetate (40ml). The filtrate was concentrated *in vacuo* to afford a pale pink foam containing (2*S*,3*S*,4*R*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2',3'-dihydroxy-4'-methoxyphenyl)pyrrolidine **15** and (2*S*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2',3'-dihydroxy-4'-methoxyphenyl) pyrrolidine **16** in a ratio of *ca.* 15:1 (as determined by ^1H NMR (500MHz)) (230mg, 99%). The following spectroscopic data was recorded for the product mixture containing **15** as the major isomer; $[\alpha]_D^{22}$ -24.0 (c 1.0, $CHCl_3$); R_f 0.25 (15:1 v/v CH_2Cl_2 : MeOH); υ_{max}/cm^{-1} ($CHCl_3$) 3552s, 3022m, 3008m, 1741s, 1733s, 1635s, 1514m, 1489m, 1449m, 1420s, 1369m, 1289s, 1150s, 1098m; δ_H (500MHz; $CDCl_3$) 1.37 (9H, s, $C(CH_3)_3$), 2.47 (2H, d, *J*6Hz, $CH_2CO_2Bu^t$), 3.02-3.10 (1H, m, $CHCH_2CO_2Bu^t$), 3.39-3.47 (1H, m, NCH_2CH), 3.74-3.91 (8H, m, CO_2CH_3, $ArOCH_3$ and NCH_2), 4.48 (1H, d, *J*9.5Hz, $NCHCO_2Me$), 5.49, 5.72 (2 x 1H, 2 x s, 2 x OH), 6.44 (1H, d, *J*8.5Hz, Ar-H), 6.71 (1H, d, *J*8.5Hz, Ar-H), 7.31-7.67 (3H, m, Ph-H); δ_C (50.3MHz; $CDCl_3$) 27.82 ($C(CH_3)_3$), 36.41 ($CH_2CO_2Bu^t$), 43.43, 43.68 ($CHCH_2CO_2Bu^t$, Ar-CH) 52.35 (CO_2CH_3), 55.06 ($ArOCH_3$), 64.57 ($CHCO_2CH_3$), 80.98 ($C(CH_3)_3$), 103.34 (ArCH), 116.22 (Ar-C_{ipso}), 118.34, 127.87, 128.34, 130.67 (ArCH), 133.00, 135.48, 143.45, 146.69 (Ar-C_{ipso}), 169.74 (NC=O), 171.15, 172.71 (CO_2Bu^t and CO_2CH_3); *m/z* (DCI, NH_3) 486 (MH^+, 16%), 430 (17), 105 (100); Found: MH^+ 486.2128, $C_{26}H_{32}NO_8$ requires 486.2128.

(2*S*,3*S*,4*R*)-(2'*Z*,4'*E*)-*N*-Benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2'-(dimethyl-5'-methoxyhexa-2',4'-dien-1',6'-oate))pyrrolidine 17

To a vigorously stirred solution of a mixture of (2*S*,3*S*,4*R*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2',3'-dihydroxy-4'-methoxyphenyl)pyrrolidine **15** and (2*S*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2',3'-dihydroxy-4'-methoxyphenyl)pyrrolidine **16** (15:1) (44mg, 0.091mmol) in dry dichloromethane (1ml) at room temperature was added Fétizon's reagent[12] (260mg) in one portion. After 15 min. the mixture was filtered through a small plug of $MgSO_4$ (*ca.* 5mm) in a Pasteur pipette. The plug was washed with dry dichloromethane (2x1ml). The deep red filtrate was cooled to 0°C and treated with dry methanol (1ml) followed by lead tetraacetate (53mg, 0.144mmol). The reaction mixture was stirred at 0°C for 30 min. then concentrated *in vacuo* to give an orange residue. The crude product was dissolved in diethyl ether (20ml) and washed with water (10ml) and saturated brine (10ml). The organic extract was dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by preparative HPLC on silica gel (eluting with 3:1 v/v dichloromethane : ethyl acetate) afforded (2*S*,3*S*,4*R*)-(2'*Z*,4'*E*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2'-(dimethyl-5'-methoxyhexa-2',4'-dien-1',6'-oate) pyrrolidine **17** (40mg, 81%) as a colourless gum, $[\alpha]_D^{23}$ -9.1 (c 0.5, $CHCl_3$); R_f 0.65 (2:1 v/v CH_2Cl_2 : EtOAc); λ_{max} ($CHCl_3$) 304nm, (ε 8240); υ_{max}/cm^{-1} ($CDCl_3$) 1728s, 1631s, 1436m, 1369s, 1248m, 1152s; δ_H (200MHz; $CDCl_3$) 1.42 (9H, s, $C(C\underline{H}_3)_3$), 2.47-2.58 (2H, m, $C\underline{H}_2CO_2Bu^t$), 2.95-3.91 (16H, m, $NC\underline{H}_2$, $NCH_2C\underline{H}$, $C\underline{H}CH_2CO_2Bu^t$, 4 x $C\underline{H}_3$), 4.43 (1H, d, *J* 9Hz, $C\underline{H}CO_2CH_3$), 7.06 (1H, d, *J* 11.5Hz, C<u>H</u> diene), 7.34-7.50 (3H, m, Ar-<u>H</u>), 7.56-7.70 (3H, complex, Ar-<u>H</u>, C<u>H</u> diene); δ_C (50.3MHz; $CDCl_3$) 28.18 ($C(\underline{C}H_3)_3$), 36.71 ($\underline{C}H_2CO_2Bu^t$), 42.96 ($\underline{C}HCH_2CO_2Bu^t$), 49.06 ($NCH_2\underline{C}H$), 51.92, 52.59, 52.78 (3 x $CO_2\underline{C}H_3$), 55.34 ($N\underline{C}H_2$), 56.14 ($C(O\underline{C}H_3)CO_2$), 64.27 ($N\underline{C}HCO_2Me$), 81.15 ($\underline{C}(CH_3)_3$), 108.10 (<u>C</u>H diene), 125.94 (Ar-$\underline{C}_{ipso}$), 127.87, 128.41, 130.76 (Ar<u>C</u>H), 135.36 (Ar-$\underline{C}_{ipso}$), 136.92 (<u>C</u>H diene), 151.04 ($\underline{C}(OCH_3)CO_2$), 162.94, 167.09, 169.48, 170.45, 172.07 ($N\underline{C}$=O, $\underline{C}O_2Bu^t$, 3 x $\underline{C}O_2CH_3$); *m/z* (DCI, NH_3) 546 (MH^+, 3%), 490 (4), 105 (100); (Found MH^+ 546.2340, $C_{28}H_{36}NO_{10}$ requires 546.2339).

(2*S*,3*S*,4*R*)-3-Methylenecarboxy-4-(3'-(2'-pyrone-6'-carboxylic acid))pyrrolidine-2-carboxylic acid hydrochloride 18

A solution of (2*S*,3*S*,4*R*)-(2'*Z*,4'*E*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2'-(dimethyl-5'-methoxyhexa-2',4'-dien-1',6'-oate)pyrrolidine **17** (35mg, 0.064mmol) in concentrated hydrochloric acid (1ml) was heated under reflux for 1h. The mixture was concentrated *in vacuo* and redissolved in water. Filtration through a small plug of cotton wool in a Pasteur pipette followed by concentration *in vacuo* afforded (2*S*,3*S*,4*R*)-3-methylenecarboxy-4-(3'-(2'-pyrone-6'-carboxylic acid)) pyrrolidine-2-carboxylic acid hydrochloride **18** (22mg, 99%) as a brown gum, $[\alpha]_D^{25}$ -38.4 (c 0.45, H_2O); λ_{max} (H_2O) 306nm, (ε 9560); δ_H (400MHz; D_2O) 2.73, 2.94 (2 x 1H, ABX, J_{AB}18Hz, J_{AX}7Hz, J_{BX}5Hz, $C\underline{H}_2CO_2H$), 3.10-3.26 (1H, m, $C\underline{H}CH_2CO_2H$), 3.50 (1H, q, J_{AB}9Hz, $NCH_2C\underline{H}$), 3.74 (2H, d, *J*9Hz, $NC\underline{H}_2$), 4.34 (1H, d, *J*9Hz, $NC\underline{H}CO_2H$), 7.23 (1H, d, *J*7Hz, $\underline{H}C$=$C(CO_2H)O$), 7.66 (1H, d, *J*7Hz, $\underline{H}C$=$C(CO_2C)C$); NOe experiment: irradiation at 2.73ppm ($C\underline{H}(H)CO_2$) caused a 3.5% enhancement at 4.34ppm ($NC\underline{H}CO_2H$) and a 4.5% enhancement at 3.50ppm ($NCH_2C\underline{H}$); irradition at 2.94ppm caused a 5.6% enhancement at 4.34ppm and 5.6% enhancement at 3.50ppm; no enhancements were observed at either 7.23ppm or 7.66ppm; δ_C

(100.6MHz; D_2O) 35.97 ($\underline{C}H_2CO_2H$), 41.96, 46.75 ($NCH_2\underline{C}H$, $\underline{C}HCH_2CO_2H$), 48.18 ($N\underline{C}H_2$), 67.71 ($N\underline{C}HCO_2H$), 111.84 ($H\underline{C}$=C(CO_2H)O), 129.20 (HC=$\underline{C}$(CO_2C)C), 143.45 ($H\underline{C}$=C(CO_2C)C), 163.10, 175.49 ($\underline{C}O_2H$), sample too weak to detect all quarternary carbons; *m/z* (Electrospray, positive ion) 334 (MNa^+, 13%), 312 (MH^+, 100).

***Allo*-acromelic acid A 19**

A solution of (2*S*,3*S*,4*R*)-3-methylenecarboxy-4-(3'-(2'-pyrone-6'-carboxylic acid))pyrrolidine-2-carboxylic acid hydrochloride **18** (12mg, 0.037mmol) was dissolved in concentrated aqueous ammonia solution (1ml) and aged overnight at room temperature. Concentration *in vacuo* afforded *allo*-acromelic acid A **19** (11.5mg, 100%) as a brown gum, $[\alpha]_D^{23}$ -9.1 (c 0.5, $CHCl_3$); δ_H (270MHz; D_2O) 2.35, 2.67 (2 x 1H, ABX, J_{AB} 14.5Hz, J_{AX} 9Hz, J_{BX} 4Hz, $C\underline{H}_2CO_2H$), 2.79-2.95 (1H, m, $C\underline{H}CH_2CO_2H$), 3.30-3.74 (3H, complex, $NC\underline{H}_2$, $NCH_2C\underline{H}$), 3.91 (1H, d, *J* 9.5Hz, $NC\underline{H}CO_2H$), 6.93 (1H, d, *J* 7Hz, $\underline{H}C$=C(CO_2H)NH), 7.59 (1H, d, *J* 7Hz, $\underline{H}C$=C(CONH)C); δ_C (67MHz; D_2O) 41.04 ($\underline{C}H_2CO_2H$), 44.62, 46.51 ($NCH_2\underline{C}H$, $\underline{C}HCH_2CO_2H$), 48.91 ($N\underline{C}H_2$), 66.48 ($N\underline{C}HCO_2H$), 110.00 ($H\underline{C}$=C(CO_2H)NH), 132.81 (HC=$\underline{C}$(CONH)C), 139.50 ($H\underline{C}$=C(CONH)C), 141.79 (HC=$\underline{C}$(CO_2H)NH), sample too weak to distinguish carbonyl signals; *m/z* (Electrospray, positive ion) 333 (MNa^+, 12%), 311 (MH^+, 100).

(2*S*,3*S*)-*N*-Benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(2',3'-dibenzyloxy-4'-methoxyphenyl)-[4,5]-dehydropyrrolidine 20

To a stirred solution of (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2',3'-dibenzyloxy-4'-methoxyphenyl)-[4,5]-dehydropyrrolidine **14** (790mg, 1.19mmol) in methanol (15ml) at room temperature was added sodium borohydride (2.71g, 71.4mmol) in 6 equal portions over 24h. (Note: A further portion of methanol (6ml) was added after 12h). The reaction mixture was poured into saturated aqueous ammonium chloride solution (180ml) and the resulting mixture was extracted with ethyl acetate (5 x 100ml), the combined extracts being washed with 0.1M aqueous hydrochloric acid (200ml), saturated aqueous sodium bicarbonate solution (200ml) and brine (200ml). The separated organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo* and the residue was purified by flash chromatography on silica gel (eluting with 5:4 v/v dichloromethane : ethyl acetate) to give (2*S*,3*S*)-*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(2',3'-dibenzyloxy-4'-methoxyphenyl)-[4,5]-dehydropyrrolidine **20** as a colourless syrup (589mg, 78%); R_f 0.45 (1:1 v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{23}$ -21.9 (c 1.075, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3363brw, 2983m, 1722s, 1598s, 1575s, 1494s, 1448s, 1440s, 1423s, 1371s, 1292s, 1249m, 1152s, 1111s, 1080s, 1030m, 741m; δ_H (300MHz; $CDCl_3$) 1.49 (9H, s, $CO_2C(C\underline{H}_3)_3$), 2.25 (1H, *ca* dd, *J* 17, 10Hz, $C\underline{H}_2CO_2Bu^t$), 2.56 (1H, *ca* dd, *J* 17, 3Hz, $C\underline{H}_2CO_2Bu^t$), 3.36-3.45 (1H, m, $C\underline{H}CH_2CO_2Bu^t$), 3.78-3.98 (5H, complex, $C\underline{H}_2OH$, Ar-$OC\underline{H}_3$), 4.31-4.38 (1H, m, $O\underline{H}$), 4.53-4.63 (1H, m, $C\underline{H}CH_2OH$), 4.92-5.10 (4H, complex, 2 x Ph-$C\underline{H}_2$), 6.70, 6.90 (2H, ABq, *J* 9Hz, 2 x Ar-C$\underline{H}$), 7.07-7.52 (16H, complex, Ph-C$\underline{H}$, NC$\underline{H}$=C); δ_C (50.3MHz; $CDCl_3$) 28.07 ($CO_2C(\underline{C}H_3)_3$), 38.73 ($\underline{C}H_2CO_2Bu^t$), 42.78 ($\underline{C}HCH_2CO_2Bu^t$), 56.03 (Ar-$O\underline{C}H_3$), 66.21 ($\underline{C}H_2OH$, $\underline{C}HCH_2OH$), 75.14, 75.42 (2 x Ph-$\underline{C}H_2$), 81.54 ($CO_2\underline{C}(CH_3)_3$), 107.92, 119.96, 122.70, 122.90, 127.32,

128.24, 128.47, 128.68, 128.92, 131.12, 134.97, 137.15, 137.51, 142.02 (CH=C, CH=C, Ar-CH), 151.31, 153.68 (Ar-C_{ipso}), 169.26, 171.47 (2 x C=O); *m/z* (APCI+) 638 (28%), 636 (MH^+, 100), 618 (23), 582 (21), 581 (62), 580 (60); (Found MH^+ 636.2960, $C_{39}H_{42}NO_7$ requires 636.2961).

(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(2',3'-dihydroxy-4'-methoxyphenyl)pyrrolidine 21 and (2*S*,3*S*,4*R*)-*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(2',3'-dihydroxy-4'-methoxyphenyl)pyrrolidine 22

A solution of (2*S*,3*S*)-*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(2',3'-dibenzyloxy-4'-methoxyphenyl)-[4,5]-dehydropyrrolidine **20** (396mg, 0.62mmol) in 10:1 v/v hexane : 1,4-dioxane (15ml) containing palladium black (150mg, 1.41mmol) was stirred under an atmosphere of hydrogen in a Fisher-Porter apparatus at 4 atmospheres for 46h at room temperature. The reaction mixture was filtered through a magnesium sulfate plug and evaporated to dryness *in vacuo*, to give an 11:1 mixture of (2*S*,3*S*,4*S*)-*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(2',3'-dihydroxy-4'-methoxyphenyl)pyrrolidine **21** and (2*S*,3*S*,4*R*)-*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(2',3'-dihydroxy-4'-methoxyphenyl) pyrrolidine **22** as a colourless oil (284mg, 100%) which was used in the next step without further purification. Limited spectroscopic data for the major isomer (2*S*,3*S*,4*S*)-*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(2',3'-dihydroxy-4'-methoxyphenyl)pyrrolidine **21** given only; R_f 0.25 (1:1v/v CH_2Cl_2 : EtOAc); υ_{max}/cm^{-1} ($CHCl_3$) 3552s, 3370brw, 3012w, 1723s, 1602s, 1576m, 1513s, 1429s, 1290s, 1254s, 1153s, 1097s; δ_H (300MHz; $CDCl_3$) 1.42 (9H, s, $CO_2C(CH_3)_3$), 2.05-2.25 (2H, 8 line m, $CHCH_2CO_2Bu^t$), 2.74-2.88 (1H, m, $CHCH_2CO_2Bu^t$), 3.64-4.18 (9H, complex, $CHCH_2OH$, Ar-OCH_3, NCH_2, NCH_2CH, $CHCH_2OH$), 4.84 (1H, brs, OH), 5.98, 6.08 (2 x 1H, 2 x s, 2 x Ar-OH), 6.31, 6.39 (2H, ABq, *J* 9Hz, 2 x Ar-H), 7.27-7.60 (5H, complex, Ar-H); δ_C (50.3MHz; $CDCl_3$) 27.90 ($CO_2C(CH_3)_3$), 34.70 ($CHCH_2CO_2Bu^t$), 38.44 ($CHCH_2CO_2Bu^t$), 40.66 (NCH_2CH), 55.73 (NCH_2), 56.02 (Ar-OCH_3), 65.46 ($CHCH_2OH$), 65.61 (CH_2OH), 81.28 ($CO_2C(CH_3)_3$), 103.45, 117.68, 119.10, 127.23, 128.44, 128.64, 130.53, 133.18 (Ar-CH), 136.53, 142.75, 146.47, (Ar-C_{ipso}), 172.65 (2 x C=O); *m/z* (APCI+) 458 (MH^+, 100%), 440 (23), 402 (28), 384 (8); (Found MH^+ 458.2185, $C_{25}H_{32}NO_7$ requires 458.2179).

(2*S*,3*S*,4*S*)-(2'*Z*,4'*E*)-*N*-Benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(2'-(dimethyl-5'-methoxyhexan-2',4'-dien-1',6'-oate))pyrrolidine 24

To a solution of an 11:1 mixture of (2*S*,3*S*,4*S*)-*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(2',3'-dihydroxy-4'-methoxyphenyl)pyrrolidine **21** and its C-4 epimer (335mg, 0.733mmol) in methanol (40ml) was added lead tetraacetate (636mg, 1.44mmol) in one portion and the reaction was stirred at room temperature for 1h. After dilution with dichloromethane (70ml) the organic phase was washed with saturated aqueous sodium bicarbonate solution (50ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield an inseparable 11:1 mixture of (2*S*,3*S*,4*S*)-(2'*Z*,4'*E*)-*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(2'-(dimethyl-5'-methoxyhexan-2',4'-dien-1',6'-oate))pyrrolidine **24** and its C-4 epimer (360mg, 95%) as a colourless oil without further purification. The following limited spectroscopic

data was obtained for the major isomer (2*S*,3*S*,4*S*)-(2'*Z*,4'*E*)-*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(2'-(dimethyl-5'-methoxyhexan-2',4'-dien-1',6'-oate))pyrrolidine **24**; R_f 0.25 (1:1 v/v CH_2Cl_2 : EtOAc); υ_{max}/cm^{-1} ($CHCl_3$) 3695w, 3606w, 3012w, 3378brw, 2983w, 2954w, 1724s, 1613s, 1601s, 1578w, 1435s, 1422s, 1370s, 1153s, 1097w; δ_H (300MHz; $CDCl_3$) mixture of rotamers - major rotamer assigned only; 1.40 (9H, s, $CO_2C(C\underline{H}_3)_3$), 2.34 (2H, d, *J* 8Hz, $CHC\underline{H}_2CO_2Bu^t$), 2.63-2.78 (1H, m, $C\underline{H}CH_2CO_2Bu^t$), 3.46-3.98 (14H, complex, $CHC\underline{H}_2OH$, C=C-$OC\underline{H}_3$, $NC\underline{H}_2$, $NCH_2C\underline{H}$, 2 x $CO_2C\underline{H}_3$), 4.02-4.11 (1H, m, $NC\underline{H}CH_2OH$), 4.54-4.69 (1H, brs, O<u>H</u>), 6.72 (1H, d, *J* 13Hz, C<u>H</u> diene), 7.23 (1H, d, *J* 13Hz, C<u>H</u> diene), 7.30-7.56 (5H, complex, Ar-<u>H</u>); δ_C (50.3MHz; $CDCl_3$) major rotamer assigned only; 27.92 ($CO_2C(\underline{C}H_3)_3$), 34.52 ($CH\underline{C}H_2CO_2Bu^t$), 40.66 ($\underline{C}HCH_2CO_2Bu^t$), 43.14 ($NCH_2\underline{C}H$), 52.00, 52.55 (2 x $CO_2\underline{C}H_3$), 54.48 ($N\underline{C}H_2$), 56.02 (C=C-$O\underline{C}H_3$), 65.51 ($\underline{C}HCH_2OH$), 65.79 ($\underline{C}H_2OH$), 81.14 ($CO_2\underline{C}(CH_3)_3$), 107.89 (<u>C</u>H diene), 127.26, 128.57 (Ar<u>C</u>H), 129.74 (<<u>C</u>> diene), 130.45, 133.63 (<u>C</u>H diene, Ar<u>C</u>H), 136.50 (Ar-$\underline{C}_{ipso}$), 150.29 (C=$\underline{C}(OCH_3)CO_2CH_3$), 167.91, 171.50, 172.35 (2 x $\underline{C}O_2CH_3$, $\underline{C}O_2Bu^t$, N<u>C</u>=O); *m/z* (APCI+) 541 (6%), 540 (7), 520 (7), 518 (MH^+, 63), 501 (5), 500 (24), 463 (12), 462 (100), 444 (7); (Found M-C_4H_8 461.1682, $C_{23}H_{27}NO_9$ requires 461.1686).

(2*S*,3*S*,4*S*)-(2'*Z*,4'*E*)-*N*-Benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2'-(dimethyl-5'-methoxyhexan-2',4'-dien-1',6'-oate))pyrrolidine 25

To an 11:1 mixture of (2*S*,3*S*,4*S*)-(2'*Z*,4'*E*)-*N*-benzoyl-2-hydroxymethyl-3-methoxycarbonylmethyl-4-(2'-(dimethyl-5'-methoxyhexan-2',4'-dien-1',6'-oate))pyrrolidine **24** and its C-4 epimer (75mg, 0.145mmol) in acetone (2.5ml) at 0°C was added Jones reagent (1ml) dropwise (preparation of the Jones reagent: To a solution of chromium trioxide (143mg, 1.43mmol) in distilled water (2ml) at 0°C was added concentrated sulfuric acid (125µl, 2.25mmol) dropwise with swirling). The reaction was warmed to room temperature and stirred for 16h. The mixture was poured onto saturated brine (10ml) and the organics were extracted with chloroform (5 x 10ml). The combined organic phases were dried ($MgSO_4$), filtered and evaporated to dryness *in vacuo*. To a solution of the crude carboxylic acids in 4:1 v/v benzene : methanol (3ml) was added trimethylsilyldiazomethane (132µl, 0.23mmol) and after stirring the mixture at room temperature for 1h, the reaction was quenched by the addition of glacial acetic acid (3 drops). After concentration *in vacuo*, partial purification by flash chromatography on silica gel (eluting with 12:1v/v dichloromethane : ethyl acetate) gave an 11:1 mixture of (2*S*,3*S*,4*S*)-(2'*Z*,4'*E*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2'-(dimethyl-5'-methoxyhexan-2',4'-dien-1',6'-oate))pyrrolidine **25** and its C-4 epimer as a colourless syrup (43mg, 54%). The following limited spectroscopic data was obtained for the major isomer (2*S*,3*S*,4*S*)-(2'*Z*,4'*E*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2'-(dimethyl-5'-methoxyhexan-2',4'-dien-1',6'-oate))pyrrolidine **25**; R_f 0.25 (9:1v/v CH_2Cl_2 : EtOAc); υ_{max}/cm^{-1} ($CHCl_3$) 2955w, 1725brs, 1633s, 1580m, 1436s, 1422s, 1370s, 1339s, 1182s, 1154s, 1124s, 1028w, 929m; δ_H (300MHz; $CDCl_3$) mixture of rotamers - major resonances assigned only, 1.41 (9H, s, $CO_2C(C\underline{H}_3)_3$), 2.38 (2H, d, *J* 7Hz, $CHC\underline{H}_2CO_2Bu^t$), 2.94-3.05 (1H, m, $C\underline{H}CH_2CO_2Bu^t$), 3.60-4.05 (15H, complex, 3 x $CO_2C\underline{H}_3$, C=C-$OC\underline{H}_3$, $NC\underline{H}_2$, $NCH_2C\underline{H}$), 4.37 (1H, d, *J* 6Hz, $NC\underline{H}CO_2CH_3$), 6.83 (1H, d, *J* 11Hz, C<u>H</u> diene), 7.30-7.62 (6H, complex, Ar-<u>H</u>, C<u>H</u> diene); δ_C (50.3MHz; $CDCl_3$) mixture of rotamers - major resonances assigned only, 27.85 ($CO_2C(\underline{C}H_3)_3$), 34.43 ($CH\underline{C}H_2CO_2Bu^t$), 41.82 ($\underline{C}HCH_2CO_2Bu^t$), 43.58 ($NCH_2\underline{C}H$), 51.91, 52.38, 55.79 (3 x $CO_2\underline{C}H_3$, C=C-

$O\underline{C}H_3$), 52.76 ($N\underline{C}H_2$), 63.63 ($N\underline{C}HCO_2CH_3$), 81.07 ($CO_2\underline{C}(CH_3)_3$), 107.94 (<u>C</u>H diene), 127.51, 128.41, 130.52, 134.03 (Ar<u>C</u>H, <u>C</u>H diene), 135.80 (Ar-$\underline{C}_{ipso}$), 150.36 ($C=\underline{C}(OCH_3)CO_2CH_3$), 162.99, 167.57, 169.79, 170.83, 172.19 (3 x $\underline{C}O_2CH_3$, $\underline{C}O_2Bu^t$, $N\underline{C}=O$); *m/z* (APCI+) 546 (MH^+, 18%), 492 (4), 491 (28), 490 (100), 124 (14), 122 (50); (Found MH^+ 546.2340, $C_{28}H_{36}NO_{10}$ requires 546.2339).

(2*S*,3*S*,4*S*)-3-Methylenecarboxy-4-(3'-(2'-pyrone-6'-carboxylic acid))pyrrolidine-2-carboxylic acid hydrochloride 26

A solution of an 11:1 mixture of (2*S*,3*S*,4*S*)-(2'*Z*,4'*E*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2'-(dimethyl-5'-methoxyhexan-2',4'-dien-1',6'-oate))pyrrolidine **25** and its C-4 epimer (175mg, 0.32mmol) in 6M hydrochloric acid (12ml) was heated under reflux for 1h. After cooling to room temperature, the solvent was removed *in vacuo* to give an 11:1 mixture of (2*S*,3*S*,4*S*)-3-methylenecarboxy-4-(3'-(2'-pyrone-6'-carboxylic acid))pyrrolidine-2-carboxylic acid hydrochloride **26** and its C-4 epimer (110mg) as a beige solid. The following limited spectroscopic data was obtained for the major isomer (2*S*,3*S*,4*S*)-3-methylenecarboxy-4-(3'-(2'-pyrone-6'-carboxylic acid))pyrrolidine-2-carboxylic acid hydrochloride **26**; υ_{max}/cm^{-1} (KBr disc) 3900-2300brs, 1732s, 1714s, 1700s, 1558m, 1204m; δ_H (300MHz; D_2O) 2.17 (1H, *ca.* dd, *J* 17, 10Hz, $C\underline{H}_2CO_2H$), 2.58 (1H, *ca.* dd, *J* 17, 5Hz, $C\underline{H}_2CO_2H$), 3.02-3.14 (1H, m, $C\underline{H}CH_2CO_2H$), 3.47-3.72 (3H, complex, $NC\underline{H}_2$, $NCH_2C\underline{H}$), 4.34 (1H, d, *J* 9Hz, $NC\underline{H}CO_2H$), 7.04 (1H, d, *J* 7Hz, Ar-<u>H</u>), 7.35 (1H, d, *J* 7Hz, Ar-<u>H</u>); δ_C (125.8MHz; D_2O) 33.34 ($\underline{C}H_2CO_2H$), 41.30 ($\underline{C}HCH_2CO_2H$), 42.71 ($NCH_2\underline{C}H$), 47.32 ($N\underline{C}H_2$), 63.96 ($N\underline{C}HCO_2H$), 111.52 ($H\underline{C}=C(CO_2H)O$), 128.77 (HC=<u>C</u><), 144.24 ($H\underline{C}=C<$), 149.19 ($HC=\underline{C}(CO_2H)O$), 162.42, 163.09, 170.78, 175.00 (3 x $\underline{C}O_2H$, $\underline{C}O_2C$); *m/z* (Electrospray, negative ion) 324 (6%), 311 (9), 310 ($M-H^-$, 100), 281 (4), 267 (6), 266 (33), 265 (3).

Acromelic acid A 1

A solution of an 11:1 mixture of (2*S*,3*S*,4*S*)-3-methylenecarboxy-4-(3'-(2'-pyrone-6'-carboxylic acid))pyrrolidine-2-carboxylic acid hydrochloride **26** and its C-4 epimer (110mg, 0.35mmol) in concentrated aqueous ammonia solution (sp. gr. *ca.* 0.91) (12ml) was aged at room temperature for 48h. Concentration *in vacuo* afforded a brown gum which was partially purified by ion-exchange chromatography using Dowex® 50WX8 to give an 11:1 mixture of acromelic acid A **1** and its C-4 epimer (100mg, 100% from **25**) as a brown glass. The mixture was dissolved in water (2ml), filtered through a pad of activated charcoal (1x1cm) and the solvent removed *in vacuo* to give a colourless residue which was purified by column chromatography on cellulose (eluting with 3:1 v/v acetonitrile : water) to yield acromelic acid A **1** (60mg, 60% from **25**) as a white, crystalline solid; m.p. >320°C; $[\alpha]_D^{23}$ +27.5 (c 0.28, H_2O) (Lit.[2b] $[\alpha]_D$+27.8 (c 0.35, H_2O)); υ_{max}/cm^{-1} (KBr disc) 3760-2370brs, 1724s, 1714s, 1693s, 1614brs, 1385brs, 1193w, 1131m, 786w; δ_H (500MHz; D_2O) 2.18 (1H, dd, *J* 17, 10Hz, $C\underline{H}_2CO_2H$), 2.60 (1H, dd, *J* 17, 5Hz, $C\underline{H}_2CO_2H$), 3.09-3.15 (1H, m, $C\underline{H}CH_2CO_2H$), 3.61-3.69 (2H, m, $NC\underline{H}_2$), 3.73-3.78 (1H, m, $NCH_2C\underline{H}$), 4.06 (1H, d, *J* 7.5Hz, $NC\underline{H}CO_2H$), 6.88 (1H, d, *J* 7Hz, <u>H</u>C=C-NHCO), 7.46 (1H, d, *J* 7Hz, <u>H</u>C=CC(O)NH); δ_C (125.8MHz; D_2O) 35.45 ($\underline{C}H_2CO_2H$), 42.62, 42.95 ($\underline{C}HCH_2CO_2H$, $NCH_2\underline{C}H$), 48.17 ($N\underline{C}H_2$), 66.45 ($N\underline{C}HCO_2H$), 109.62 ($H\underline{C}=C$-

NHCO), 130.43 (C=C-C(O)NH), 140.20 (C=C-NHCO), 143.30 (HC=C-C(O)NH), 163.85, 166.99, 174.12, 176.32 (4 x C=O); *m/z* (Electrospray, negative ion) 310 (10%), 309 (M-H$^-$, 75), 222 (10), 172 (11), 154 (100), 132 (8).

(2*S*,3*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(3',4'-dibenzyloxy-2'-methoxyphenyl)-[4,5]-dehydropyrrolidine 27

To a vigorously stirred solution of (2*S*,3*R*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonyl methyl-4-trifluoromethanesulphonyloxy-[4,5]-dehydropyrrolidine **7**[7a,b] (2.240g, 4.33mmol) in degassed 1,2-dimethoxyethane (50ml), a solution of 3,4-dibenzyloxy-2-methoxyphenylboronic acid **13** (2.200g, 6.05mmol) in 1,2-dimethoxyethane (25ml), 2M aqueous sodium carbonate (25ml), lithium chloride (388mg, 9.15mmol) and tetrakis(triphenylphosphine) palladium (0) (189mg, 163μmol) were added sequentially. The stirred 2-phase system was heated under reflux under an argon atmosphere for 40min. After cooling to room temperature, the solvents were removed *in vacuo* and the residue was partitioned between dichloromethane (200ml) and a mixture of 2M aqueous sodium carbonate (100ml) and concentrated ammonium hydroxide (3ml). The separated aqueous layer was extracted with dichloromethane (3 x 200ml) and the combined extracts were washed with water (3 x 500ml), dried ($MgSO_4$), filtered and evaporated to dryness *in vacuo*. Flash chromatography on silica gel (eluting with 15:1 v/v dichloromethane : ethyl acetate) yielded (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(3',4'-dibenzyloxy-2'-methoxyphenyl)-[4,5]-dehydropyrrolidine **27** (2.135g, 74%) as a pale yellow syrup; R_f 0.65 (1:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{23}$ +24.0 (c 1.0, $CHCl_3$), λ_{max} ($CHCl_3$) 317nm, (ε 6818); υ_{max}/cm^{-1} ($CHCl_3$) 2983w, 1748s, 1724s, 1643s, 1619s, 1602s, 1528m, 1370s, 1293s, 1265s, 1230s, 1194s, 1149s, 1068s; δ_H (300MHz; $CDCl_3$) 1.51 (9H, s, $C(CH_3)_3$), 2.39 (1H, *ca.* dd, *J* 10, 16Hz, $CH_2CO_2Bu^t$), 2.67 (1H, *ca.* dd, *J* 3, 16Hz, $CH_2CO_2Bu^t$), 3.78-3.93 (7H, complex, CO_2CH_3, $CHCH_2CO_2Bu^t$, Ar-OCH_3), 4.96-5.15 (5H, complex, $CHCO_2CH_3$, 2 x $PhCH_2$), 6.72, 6.86 (2H, ABq, *J* 9Hz, 2 x Ar-CH), 7.27-7.70 (16H, complex, CH=C, Ar-H); δ_C (50.3MHz; $CDCl_3$) 28.00 ($C(CH_3)_3$), 39.47 ($CH_2CO_2Bu^t$), 44.52 (NCHCH), 52.60 (CO_2CH_3), 60.21 (Ar-OCH_3), 63.40 ($CHCO_2CH_3$), 70.96, 75.29 (2 x $PhCH_2$), 81.45 ($C(CH_3)_3$), 109.53, 119.66, 121.39, 122.32, 127.61, 128.21, 128.36, 128.53, 128.78, 131.15, (Ar-CH, NC=C, NC=C), 135.04, 136.93, 137.73, 142.55, 152.58 (Ar-C_{ipso}), 167.46, 170.64, 171.04 (CO_2CH_3, CO_2Bu^t, NC=O); *m/z* (APCI+) 687 (6%), 666 (9), 665 (35), 664 (MH^+, 24), 610 (31), 609 (63), 608 (100); (Found MH^+ 664.2910, $C_{40}H_{42}NO_8$ requires 664.2910).

(2*S*,3*S*)-*N*-Benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(3',4'-dibenzyloxy-2'-methoxyphenyl)-[4,5]-dehydropyrrolidine 28

To a stirred solution of (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(3',4'-dibenzyloxy-2'-methoxyphenyl)-[4,5]-dehydropyrrolidine **27** (1.096g, 1.65mmol) in methanol (30ml) at room temperature was added sodium borohydride (3.75g, 99mmol) in 6 equal portions over 24h. (Note: A further portion of methanol (10ml) was added after 12h). The reaction mixture was poured into saturated aqueous

ammonium chloride solution (200ml) and the resulting mixture was extracted with ethyl acetate (4 x 150ml), the combined extracts being washed with 0.1M aqueous hydrochloric acid (200ml), saturated aqueous sodium bicarbonate solution (200ml) and brine (200ml). The separated organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo* and the residue was purified by flash chromatography on silica gel (eluting with 1:1 v/v dichloromethane : ethyl acetate) to give (2*S*,3*S*)-*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(3',4'-dibenzyloxy-2'-methoxyphenyl)-[4,5]-dehydropyrrolidine **28** as a colourless syrup (782mg, 74%); R_f 0.40 (1:1 v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{23}$ -29.1 (c 1.66, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3689w, 3610w, 3349brw, 2982w, 1718s, 1599s, 1575m, 1490m, 1450s, 1413s, 1370s, 1250s, 1150s, 1070s; δ_H (300MHz; $CDCl_3$) 1.46 (9H, s, $CO_2C(CH_3)_3$), 2.34 (1H, *ca* dd, *J* 16, 11Hz, $CH_2CO_2Bu^t$), 2.62 (1H, *ca* dd, *J* 16, 3Hz, $CH_2CO_2Bu^t$), 3.38 (1H, brd, *J* 10Hz, $CHCH_2CO_2Bu^t$), 3.74 (3H, s, Ar-OCH_3), 3.80-4.01 (2H, complex, CH_2OH), 4.42-4.51, 4.55-4.63 (2 x 1H, 2 x m, OH, $CHCH_2OH$), 4.97-4.99 (2H, ABq, *J* 12Hz, Ph-CH_2), 5.06 (2H, s, Ph-CH_2), 6.69, 6.83 (2H, ABq, *J* 9Hz, 2 x Ar-H), 7.10 (1H, s, HC=C), 7.22-7.63 (15H, complex, Ph-CH); δ_C (50.3MHz; $CDCl_3$) 28.09 ($CO_2C(CH_3)_3$), 38.69 ($CH_2CO_2Bu^t$), 42.67 ($CHCH_2CO_2Bu^t$), 60.31 (Ar-OCH_3), 66.18, 66.32 (CH_2OH, $CHCH_2OH$), 70.96, 75.31 (2 x Ph-CH_2), 81.57 ($CO_2C(CH_3)_3$), 109.54, 119.70, 122.42, 122.62, 127.48, 127.62, 128.47, 128.59, 128.78, 131.33 (CH=C, CH=C, Ar-CH), 135.19, 136.90, 137.70, 142.58, 152.64 (Ar-C_{ipso}), 169.29, 171.44 (2 x C=O); *m/z* (APCI+) 638 (33%), 637 (87), 636 (MH^+, 70), 618 (11), 581 (27), 580 (100); (Found MH^+ 636.2960, $C_{39}H_{42}NO_7$ requires 636.2961).

(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(3',4'-dihydroxy-2'-methoxyphenyl)pyrrolidine 29

A solution of (2*S*,3*S*)-*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(3',4'-dibenzyloxy-2'-methoxyphenyl)-[4,5]-dehydropyrrolidine **28** (100mg, 0.16mmol) in ethyl acetate (4ml) containing palladium black (33mg, 0.31mmol) was stirred under an atmosphere of hydrogen in a Fisher-Porter apparatus at 4 atmospheres for 30h at room temperature. The reaction mixture was filtered through a magnesium sulphate plug and evaporated to dryness *in vacuo*, to give a 10:1 mixture of (2*S*,3*S*,4*S*)-*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(3',4'-dihydroxy-2'-methoxyphenyl)pyrrolidine **29** and its C-4 epimer as a colourless oil (72mg, 100%) which was used in the next step without further purification. Limited spectroscopic data for the major isomer (2*S*,3*S*,4*S*)-*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(3',4'-dihydroxy-2'-methoxyphenyl)pyrrolidine **29** given only; R_f 0.20 (1:1v/v CH_2Cl_2 : EtOAc); υ_{max}/cm^{-1} ($CHCl_3$) 3550m, 3330brw, 3156w, 2984m, 1728s, 1610s, 1575m, 1468m, 1448m, 1433m, 1374s, 1252s, 1213s, 1153s, 1045s, 912s; δ_H (300MHz; $CDCl_3$) 1.40 (9H, s, $CO_2C(CH_3)_3$), 2.02-2.23 (2H, 8 line m, $CHCH_2CO_2Bu^t$), 2.82-2.93 (1H, m, $CHCH_2CO_2Bu^t$), 3.56-4.20 (10H, complex, $CHCH_2OH$, Ar-OCH_3, NCH_2, NCH_2CH, $CHCH_2OH$, CH_2OH), 5.99-6.12 (1H, brs, Ar-OH), 6.27, 6.62 (2H, ABq, *J* 9Hz, 2 x Ar-H) 7.27-7.60 (5H, complex, Ar-H); δ_C (50.3MHz; $CDCl_3$) 27.89 ($CO_2C(CH_3)_3$), 34.83 ($CHCH_2CO_2Bu^t$), 38.05 ($CHCH_2CO_2Bu^t$), 40.51 (NCH_2CH), 55.96 (NCH_2), 60.67 (Ar-OCH_3), 64.79 (CH_2OH), 65.16 ($CHCH_2OH$), 81.26 ($CO_2C(CH_3)_3$), 111.20, 117.13, 123.68, 127.26, 128.75, 130.77 (Ar-CH), 136.06, 137.88, 144.83, 146.29 (Ar-C_{ipso}), 172.34, 172.74 (2 x C=O); *m/z* (APCI+) 464 (10%), 458 (MH^+, 83), 440 (22), 403 (8); (Found MH^+ 457.2095, $C_{25}H_{31}NO_7$ requires 457.2101).

(2*S*,3*S*,4*S*)-(2'*E*,4'*Z*)-*N*-Benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(3'-(dimethyl-2'-methoxyhexan-2',4'-dien-1',6'-oate))pyrrolidine 30

To a solution of a 10:1 mixture of (2*S*,3*S*,4*S*)-*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(3',4'-dihydroxy-2'-methoxyphenyl)pyrrolidine **29** and its C-4 epimer (425mg, 0.93mmol) in methanol (40ml) was added lead tetraacetate (824mg, 1.86mmol) in one portion and the reaction was stirred at room temperature for 30 minutes. After dilution with dichloromethane (80ml) the organic phase was washed with saturated aqueous sodium bicarbonate solution (50ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was partiallly purified by chromatography on silica gel (eluting with 1:1 v/v dichloromethane : ethyl acetate) to yield a 10:1 mixture of (2*S*,3*S*,4*S*)-(2'*E*,4'*Z*)-*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(3'-(dimethyl-2'-methoxyhexan-2',4'-dien-1',6'-oate))pyrrolidine **30** and its C-4 epimer (302mg, 63%) as a pale yellow oil. The following limited spectroscopic data was obtained for the major isomer (2*S*,3*S*,4*S*)-(2'*E*,4'*Z*)-*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(3'-(dimethyl-2'-methoxyhexan-2',4'-dien-1',6'-oate))pyrrolidine **30**; R_f 0.30 (1:4 v/v CH_2Cl_2 : EtOAc); υ_{max}/cm^{-1} ($CHCl_3$) 3694w, 3610w, 3002w, 1724s, 1602s, 1578w, 1448m, 1422s, 1370m, 1152s; δ_H (300MHz; $CDCl_3$) mixture of rotamers - major rotamer assigned only; 1.46 (9H, s, $CO_2C(C\underline{H}_3)_3$), 2.33-2.52 (2H, 8 line m, $CHC\underline{H}_2CO_2Bu^t$), 2.75-2.87 (1H, m, $C\underline{H}CH_2CO_2Bu^t$), 3.37 (3H, s, C=C-$OCH_3$), 3.56-4.05 (12H, complex, $CHC\underline{H}_2OH$, $NC\underline{H}_2$, $NCH_2C\underline{H}$, 2 x $CO_2C\underline{H}_3$, $C\underline{H}CH_2OH$), 4.22-4.34 (1H, brs, O<u>H</u>), 5.79 (1H, d, *J* 15Hz, C<u>H</u> diene), 6.41 (1H, d, *J* 15Hz, C<u>H</u> diene), 7.32-7.58 (5H, complex, Ar-<u>H</u>); δ_C (50.3MHz; $CDCl_3$) major rotamer assigned only; 27.89 ($CO_2C(\underline{C}H_3)_3$), 34.59 ($CH\underline{C}H_2CO_2Bu^t$), 40.24 ($\underline{C}HCH_2CO_2Bu^t$), 41.94 ($NCH_2\underline{C}H$), 51.00, 51.76, 59.00 (2 x $CO_2\underline{C}H_3$, C=C-O$\underline{C}H_3$), 53.54 ($N\underline{C}H_2$), 64.74 ($\underline{C}HCH_2OH$), 64.90 ($\underline{C}H_2OH$), 81.17 ($CO_2\underline{C}(CH_3)_3$), 122.48 (<u>C</u>H diene), 127.62, 128.30 (Ar-<u>C</u>H), 129.27 (<<u>C</u>> diene), 130.59 (Ar-<u>C</u>H), 135.99, 143.82 (<<u>C</u>> diene, Ar-$\underline{C}_{ipso}$), 139.95 (<u>C</u>H diene), 163.91, 165.46, 171.58, 171.89 (2 x $\underline{C}O_2CH_3$, $\underline{C}O_2Bu^t$, N<u>C</u>=O); *m/z* (APCI+) 540 (7%), 519 (7), 518 (MH^+, 29), 500 (15), 463 (13), 462 (100), 444 (8), 124 (17), 122 (56), 105 (6); (Found MH^+ 518.2377, $C_{27}H_{36}NO_9$ requires 518.2390).

(2*S*,3*S*,4*S*)-(2'*E*,4'*Z*)-*N*-Benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(3'-(dimethyl-2'-methoxyhexan-2',4'-dien-1',6'-oate))pyrrolidine 31

To a 10:1 mixture of (2*S*,3*S*,4*S*)-(2'*E*,4'*Z*)-*N*-benzoyl-2-hydroxymethyl-3-methoxycarbonylmethyl-4-(3'-(dimethyl-2'-methoxyhexan-2',4'-dien-1',6'-oate))pyrrolidine **30** and its C-4 epimer (302mg, 0.58mmol) in acetone (6ml) at 0°C was added Jones reagent (3ml) dropwise. The reaction was stirred and warmed to room temperature for 16h. The mixture was poured onto saturated brine (50ml) and the organics were extracted with chloroform (5 x 40ml). The combined organic phases were dried ($MgSO_4$), filtered and evaporated to dryness *in vacuo*. A solution of diazomethane in diethyl ether (20ml, excess prepared from Diazald®) was added to a solution of the crude product in dichloromethane (5ml) and after stirring the mixture at room temperature for 1h, the reaction was quenched by the addition of glacial acetic acid (10 drops). After concentration *in vacuo*, partial purification by flash chromatography on silica gel (eluting with 4:1v/v dichloromethane : ethyl acetate) gave a 10:1 mixture of (2*S*,3*S*,4*S*)-(2'*E*,4'*Z*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(3'-(dimethyl-2'-methoxyhexan-2',4'-dien-1',6'-oate))pyrrolidine **31** and its C-4 epimer as a colourless syrup (177mg, 56%) and recovered starting material (40mg (yield based on recovered

starting material 64%)). The following limited spectroscopic data was obtained for the major isomer (2*S*,3*S*,4*S*)-(2'*E*,4'*Z*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(3'-(dimethyl-2'-methoxy hexan-2',4'-dien-1',6'-oate))pyrrolidine **31**; R_f 0.55 (4:1 v/v CH_2Cl_2 : EtOAc); υ_{max}/cm^{-1} ($CHCl_3$) 3005w, 2954w, 1724brs, 1634s, 1438s, 1429s, 1297s, 1186s, 1152s, 1019w; δ_H (300MHz; $CDCl_3$) mixture of rotamers - major resonances only quoted, 1.44 (9H, s, $CO_2C(C\underline{H}_3)_3$), 2.49 (2H, d, *J* 7Hz, $CHC\underline{H}_2CO_2Bu^t$), 3.03-3.13 (1H, m, $C\underline{H}CH_2CO_2Bu^t$), 3.40-3.93 (15H, complex, 3 x $CO_2C\underline{H}_3$, C=C-OC$\underline{H}_3$, NC$\underline{H}_2$, $NCH_2C\underline{H}$), 4.22 (1H, d, *J* 8Hz, $NC\underline{H}CO_2CH_3$), 5.77 (1H, d, *J* 12Hz, C$\underline{H}$ diene), 6.41 (1H, d, *J* 12Hz, C$\underline{H}$ diene), 7.29-7.56 (5H, complex, Ar-$\underline{H}$); δ_C (50.3MHz; $CDCl_3$) mixture of rotamers - major resonances only quoted, 27.88 ($CO_2C(\underline{C}H_3)_3$), 34.33 ($CH\underline{C}H_2CO_2Bu^t$), 42.25, 42.80 ($\underline{C}HCH_2CO_2Bu^t$, $NCH_2\underline{C}H$), 51.11, 51.80, 52.38, 59.02 (3 x $CO_2\underline{C}H_3$, C=C-O$\underline{C}H_3$), 52.50 (N$\underline{C}H_2$), 63.55 (N$\underline{C}HCO_2CH_3$), 81.07 ($CO_2\underline{C}(CH_3)_3$), 122.26 ($\underline{C}H$ diene), 127.61, 128.31, 130.63 (Ar-$\underline{C}H$), 128.75 ($\underline{C}$=C-OCH$_3$), 135.44 (Ar-$\underline{C}_{ipso}$), 139.96 ($\underline{C}H$ diene), 144.14 (C=$\underline{C}$(OCH$_3$)CO_2CH_3), 163.79, 165.56, 169.72, 170.81, 172.09 (3 x $\underline{C}O_2CH_3$, $\underline{C}O_2Bu^t$, N$\underline{C}$=O); *m/z* (APCI+) 601 (6%), 547 (13), 546 (MH^+, 49), 492 (6), 491 (92), 490 (100); (Found MH^+ 546.2340, $C_{28}H_{36}NO_{10}$ requires 546.2339).

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