Synthesis of the Bicyclo[4.3.1]decenone Core of CP-225,917 and CP-263,114

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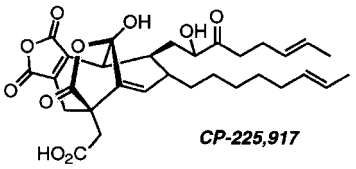
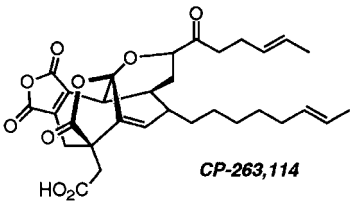
Abstract: The bicyclo[4.3.1]decenone core of the *ras*-farnesyl protein transferase inhibitors CP-225,917 and CP-263,114 is prepared in 6 steps from cyclohexanone. The key step is an intramolecular Mukaiyama aldol reaction.

The closely related natural products CP-225,917 and CP-263,114 were recently isolated by workers at Pfizer from an unidentified fungus.[1] The compounds are inhibitors of *ras*-farnesyl protein transferase,[2] and are therefore of interest in the search for novel anticancer agents.[3] Structurally, they are related to the nonadride family of natural products[4] in that they contain a nine-membered ring fused to a maleic anhydride moiety. Interestingly, they also display an anti-Bredt olefin. The combination of interesting biological activity and intriguing structure has made these compounds attractive targets for total synthesis and the groups of Davies,[5] Nicolaou[6] and Clive[7] have recently described syntheses of models of the bicyclic core. These recent reports prompt us to disclose our own preliminary results which have led to the development of a short (6 step) synthesis of the bicyclo[4.3.1]decenone core from cyclohexanone.



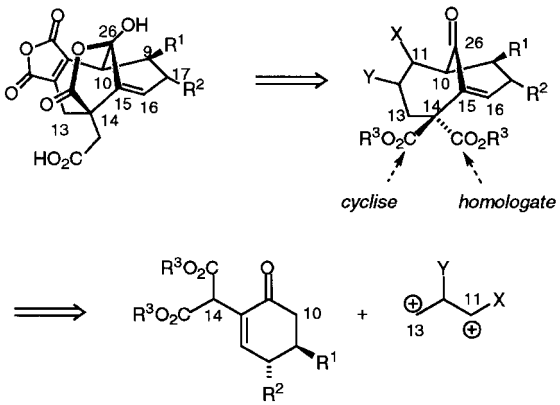
CP-225,917



CP-263,114

Our strategy (Scheme 1) has envisaged introduction of the sensitive anhydride unit late in the synthesis. The next key feature of our approach relies on the fact that, since it is present in the natural product, cyclisation of a pro-*S* carboxylic acid at C14 onto the C26 carbonyl is expected to be facile. This is presumably due to relief of ring strain in going from an sp^2 centre at C26 to an sp^3 centre. It is therefore hoped that group differentiation of a symmetrical 1,1-diester at C14 can be used to create the stereocentre at this position: cyclisation of the pro-*S* carboxylate would leave the pro-*R* acid derivative free for subsequent homologation. This strategy would also enable the anion-stabilising properties of the C14-diester to be utilised in construction of the C13-C14 bond. Further disconnection at C10-C11, using one of several conceivable methods for bond formation α- to the C26 carbonyl, would then lead to a simple cyclohexenone derivative and a suitable *bis*-electrophile. Here we report the realisation of the first major objective in this plan, the synthesis of the carbobicyclic core by bond formation at C13-C14 and C10-C11.

In order to establish methodology for the synthesis of the carbobicyclic core, our initial synthetic studies (Scheme 2) have omitted the alkyl sidechains (*i.e.* $R^1 = R^2 = H$). Thus, reaction of the lithium enolate of



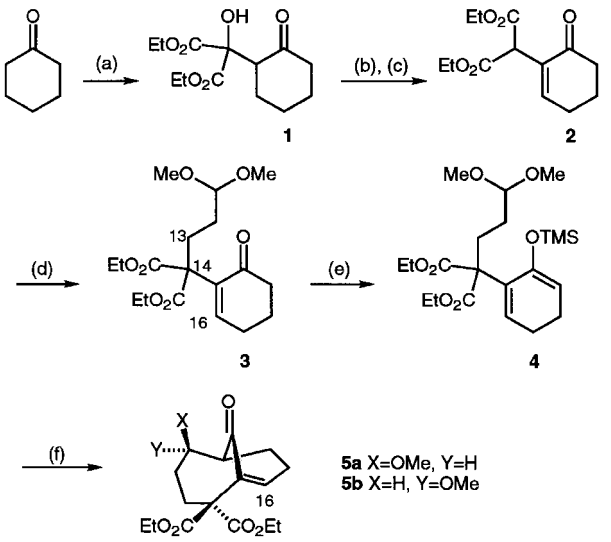
Scheme 1

cyclohexanone with diethylketomalonate gave **1** (79%). Conversion of **1** into **2** was achieved using a two step procedure: acetylation (Ac_2O, cat. TMSOTf,[8] 93% yield) followed by treatment with 1,4-diazabicyclo[2.2.2]octane (Dabco™) to effect acetate elimination and alkene isomerisation (75% yield).[9] We were pleased to find that **2** underwent clean and regioselective alkylation with commercially available 3-bromopropanal dimethylacetal, thus creating the C13-C14 bond. Conversion of **3** into the trimethylsilyl enol ether **4** then set the stage for the key ring closure step.[10] Pleasingly, treatment of **4** with $TiCl_4$ in CH_2Cl_2[11] provided the desired bicyclic product **5** (52%) as a mixture of diastereomers which could be separated by flash chromatography to give **5a** (12%) and **5b** (40%).[12] We have briefly examined alternative Lewis acids: boron trifluoride etherate gave similar overall yield (20% **5a** and 28% **5b**), while none of the cyclised product was observed when trimethylsilyl triflate was employed.

A first indication that the desired cyclisation had occurred was the upfield shift observed for H16 in the NMR spectrum (*ca.* 6.4 ppm in **5** compared to 6.95 ppm in **3**), suggesting that the enone system was not now able to adopt planarity.[13] That the desired cyclic structure had indeed been obtained was proven by HMBC and HMQC experiments on **5b**: in particular, 2-bond correlations between C10 and H11, and between C11 and H10, proved that cyclisation had occurred. The major diastereomer **5b** is tentatively assigned the relative configuration shown based on NOE studies in conjunction with molecular mechanics calculations.[14]

In summary, we have developed a short synthesis (6 steps from cyclohexanone) of the bicyclic core of the natural products CP-225,917 and CP-263,114 utilising a Mukaiyama aldol reaction as the key step. We are currently investigating the use of alternative *bis*-electrophile equivalents and the introduction of the C14 stereocentre *via* lactonisation onto the C26 carbonyl, as well as methods for the formation of the anhydride unit.

Acknowledgements. We thank the EPSRC and Zeneca Pharmaceuticals (CASE award to TJC) for their support of this work. We also thank Dr. J.A. Ballantine and the EPSRC Mass Spectrometry Service for accurate mass measurements. We wish to acknowledge the use of the EPSRC's Chemical Database Service at Daresbury.[15]



Scheme 2. *Reagents and conditions:* (a) (i) LDA, THF, -78°C, 1 hr (ii) Diethylketomalonate (1.1 eq), -78 to 0 °C, 12 hr, 79%; (b) TMSOTf (2 mol %), Ac_2O, 0°C, 5 min, 93%; (c) Dabco™ (2 eq), toluene, reflux, 90 min, 75%; (d) (i) NaH (1.05 eq), Bu_4NI (3 mol%), DMF, 0°C, 30 min (ii) 3-bromopropanal dimethylacetal, 60°C, 21 hr, 68%; (e) (i) LDA, THF, -78°C, 10 min (ii) TMSCl (1.8 eq), -78 °C, 4 hr, 92%; (f) $TiCl_4$, CH_2Cl_2, -78°C to RT, 15 hr (52%)

References and Notes

(1) Dabrah, T.T.; Kaneko, T.; Massefski Jr., T.; Whipple, E.B. *J. Am. Chem. Soc*. **1997**, *119*, 1594-1598.

(2) Dabrah, T.T.; Harwood Jr., H.J.; Huang, L.H.; Jankovich, N.D.; Kaneko, T.; Li, J-C.; Lindsey, S.; Moshier, P.M.; Subashi, T.A.; Therrien, M.; Watts, P.C. *J. Antibiot*. **1997**, *50*, 1-7.

(3) For a review of *ras*-farnesyl protein transferase inhibition, see: Buss, J.E.; Morsters, J.C. *Chem. Biol*. **1995**, *2*, 787-791.

(4) Barton, D.H.R.; Sutherland, J.K.; *J. Chem. Soc*. **1965**, 1769-1772, and subsequent papers.

(5) Davies, H.M.L.; Calvo, R.; Ahmed, G. *Tetrahedron Lett*. **1997**, *38*, 1737-1740.

(6) Nicolaou, K.C.; Härter, M.W.; Boulton, L.; Jandeleit, B. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 1194-1196. Nicolaou, K.C.; Postema, M.H.D.; Miller, N.D.; Yang, G. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2821-2823.

(7) Sgarbi, P.W.M.; Clive, D.L.J. *Chem. Commun*. **1997**, 2157-2158.

(8) Procopiou, P.A.; Baugh, S.P.D.; Flack, S.S.; Inglis, G.G.A. *Chem. Commun*. **1996**, 2625-2626.

(9) Far better yields were obtained with Dabco™ than with other bases (*e.g.* DBU); we believe that the alkene isomerisation step proceeds *via* a conjugate addition - elimination mechanism. Further details will be reported in due course. Data for **2**: colourless oil, R_f 0.38 (20% EtOAc-petrol); ν_{max} (film) 1732, 1681, 1640 (weak); δ_H (250 MHz, $CDCl_3$) 7.02 (1H, t, *J* 4.1, *H*C=), 4.69 (1H, d, *J* 1.0, *H*C($CO_2Et)_2$), 4.24-4.13 (4H, qd, *J* 7.1, 1.6, $2CH_2O$), 2.51-2.43 (4H, m), 2.08-2.00 (2H, m), 1.25 (6H, t, *J* 7.1, 2 x Me); δ_C (100 MHz, $CDCl_3$) 196.4 (s, C=O), 167.7 (s, 2 x CO_2R), 148.4 (d, HC=), 132.6 (s, C=), 61.4 (t, 2 x CH_2O), 50.4 (d, $CH(CO_2Et)_2$), 37.5 (t, CH_2), 25.8 (t, CH_2), 22.2 (t, CH_2), 13.7 (q, 2 x Me); HRMS (EI) Found M^+, 254.1162. $C_{13}H_{18}O_5$ requires 254.1154.

(10) A similar Mukaiyama aldol reaction has been used to make the corresponding saturated ring system, bicyclo[4.3.1]decanone: Kellner, D.; Loewenthal, H.J.E. *Tetrahedron Lett.* **1983**, *24*, 3397-3400.

(11) Mukaiyama, T. *Org. React.* **1982**, *28*, 203-331.

(12) $TiCl_4$ (240 µl of a 1M solution in CH_2Cl_2, 0.24 mmol) was added rapidly to a cooled (-78 °C) solution of **4** (100mg, 0.23 mmol) in CH_2Cl_2 (2ml) under N_2. The mixture was stirred at -78°C for 2 hours then allowed to warm slowly to room temperature over 13 hours. It was then cooled to 0 °C, quenched with saturated aqueous $NaHCO_3$ (10 ml) and extracted with ether (3 x 10 ml). The combined organic extracts were washed with H_2O (10 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica (20% EtOAc-petrol) yielded **5a** (9 mg, 12%) and **5b** (30 mg, 40%) as oils.
Data for **5a** (minor): R_f 0.28 (25% EtOAc-petrol); ν_{max} (film) / cm^{-1} 1736, 1708, 1451, 1245, 1088; δ_H (400MHz, $CDCl_3$) 6.46 (1H, dd, *J* 4.3, 7.8, HC=), 4.31-4.20 (4H, m, $2CH_2O$), 3.29 (3H, s, MeO), 3.28-3.15 (2H, m, CHCO and CHOMe), 2.36-2.21 (2H, m, CH_2), 2.09-1.56 (6H, m, 3 x CH_2), 1.28 (6H, t, *J* 7.1, 2 x Me); δ_C (100 MHz, $CDCl_3$) 204.1, 169.3, 169.2, 137.6, 135.4, 82.2, 61.8, 61.8, 59.1, 56.6, 50.6, 30.7, 27.7, 22.3, 19.4, 14.0, 13.9; m/z (EI) 324 (M^+, 0.14%), 279 (M^+-EtO, 1), 251 (M^+-CO_2Et, 5); Found M^+, 324.1554. $C_{17}H_{24}O_6$ requires 324.1573.
Data for **5b** (major): R_f 0.22 (25% EtOAc-petrol); ν_{max} (film) / cm^{-1} 1731, 1715, 1449, 1243, 1201; δ_H (500MHz, $CDCl_3$) 6.34 (1H, dd, *J* 4.2 and 7.7, HC=), 4.28-4.19 (4H, m, 2 x CH_2O), 3.30 (3H, s, CH_3O), 3.15 (1H, m, CHOMe), 2.96 (1H, m - resolution enhanced to ddd, *J* 2.6, 5.2, 8.3, CHCO), 2.33-1.90 (6H, m, $3CH_2$), 1.85 (1H, m, CH), 1.36-1.21 (7H, m, 2Me + CH_{ax}); δ_C (70 MHz, $CDCl_3$) 202.8 (s, C=O), 169.6 (s, CO_2R), 169.2 (s, CO_2R), 138.2 (s, R_2C=), 133.4 (d, HC=), 81.0 (d, CHOMe), 61.8 (t, CH_2O), 57.3 (s, $C(CO_2R)_2$), 56.3 (q, CH_3O), 51.8 (d, CHCO), 27.4 (t, CH_2), 24.9 (t, CH_2), 24.5 (t, CH_2), 21.7 (t, CH_2), 14.0 (q, Me); m/z (FAB) 347 (MNa^+, 36%), 325 (MH^+, 18), 293 (M^+-OMe, 10) 279 (M^+-OEt, 15); Found MH^+, 325.1640. $C_{17}H_{25}O_6$ requires 325.1651.

(13) Also in accord with this is the carbonyl stretching frequency in the IR spectrum: the observed values of 1708 cm^{-1} for **5a** and 1715 cm^{-1} for **5b** are similar to that reported (1710 cm^{-1}) for bicyclo[4.3.1]dec-1-en-10-one itself: Cordiner, B.G.; Vegar, M.R.; Wells, R. *Tetrahedron Lett.* **1970**, 2285-2286.

(14) Compound **5b** displayed an NOE to H11 on irradiation of H10; this interaction was not evident in the NOESY spectrum of **5a**. MM2* calculations in MacroModel 5.5 (Mohamadi, F.; Richards, N.G.J.; Guida, W.C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W.C. *J. Comput. Chem.* **1990**, *11*, 440-467) suggest that an NOE between H10 and H11 is unlikely in the preferred conformations of the compound with stereochemistry **5a**, whereas the H10-H11 distance is relatively short in **5b**.

(15) Fletcher, D.A.; McMeeking, R.F.; Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746-749.