Synthesis of β-Dimorphecolic Acid exploiting Highly Stereoselective Reduction of a Side-chain Carbonyl Group in a π-Allyltricarbonyliron Lactone Complex

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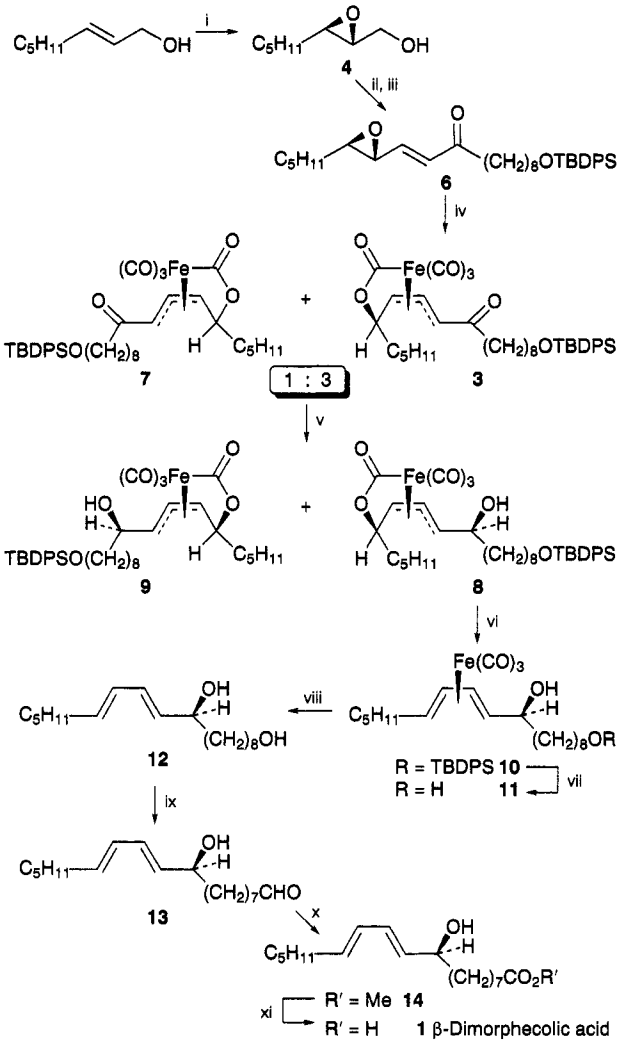
A highly stereoselective synthesis of β-dimorphecolic acid is accomplished utilising a π-allyltricarbonyliron lactone complex **3** to control the formation of all the stereochemical features of the natural product.

β-Dimorphecolic acid **1** which was first isolated from the seed oil of *Dimorphotheca aurantiaca*[1] belongs to a family of hydroxy fatty acids which possess a wealth of biological properties.[2] However, unlike its diene congener α-dimorphecolic acid, **2**, which has been demonstrated to be a calcium specific ionophore[3] and ACE inhibitor,[4] little is known about the biological properties of **1**. This lack of information is clearly related to the difficulty in cultivating the seeds and in extracting the natural product. Here, we report the first enantioselective preparation of **1** which utilises the stereoselective reduction of a carbonyl group in the side-chain of a π-allyltricarbonyliron lactone complex as a key step in the synthesis. We have previously shown that these complexes are useful precursors for the preparation of a variety of natural products.[5]

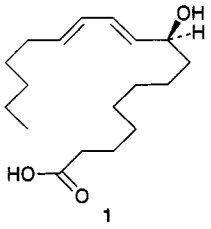
We recently reported that alkyl, phenyl, alkenylic and alkynylic groups can be transferred in a highly diastereoselective manner to π-allyltricarbonyliron lactone complexes bearing side-chain carbonyl groups using organoaluminium reagents.[6] We also noted that reagents possessing active β-hydrogens gave rise to minor amounts of a by-product in which hydrogen was transferred and the side-chain carbonyl group was reduced. This methodology compliments the established stereoselective reactions of η^4 diene–tricarbonyliron complexes described by others.[7] The relative stereochemical outcome of this 1,5-asymmetric induction was determined by comparison of ^{1}H NMR of a derivative with a sample of known configuration. The hydrogen was delivered to the carbonyl group in a similar manner to the other groups, *i.e.* addition occurred *anti* to the tricarbonyliron unit on the *S-cis* conformer of the π-allyltricarbonyliron lactone complex. This behaviour was exploited by using triisobutylaluminium to act as an efficient reducing agent for these complexes and the pattern of reactivity associated with this reagent is utilised in the work described here.

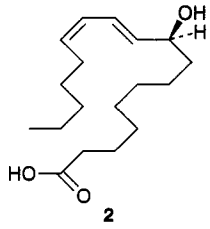
Our route to β dimorphecolic acid relied on the formation of the intermediate **3** whose preparation is delineated in Scheme 1. Application of the catalytic Sharpless asymmetric epoxidation[8] protocol to (2*E*)-oct-2-en-1-ol smoothly afforded the epoxy alcohol **4** in 70% yield. Formation of the corresponding Mosher ester[9] of **4** and comparison with racemic material indicated an e.e. >95% as determined by 500 MHz ^{1}H NMR. Oxidation of **4** to the aldehyde using *in situ* generated Collins reagent followed by Horner–Wittig homologation using the phosphonate **5**,† prepared according to the methodology of Grieco,[10] provided exclusively the epoxy enone **6**. Treatment of **6** with $Fe_2(CO)_9$ in THF[11] gave two diastereoisomeric π-allyltricarbonyliron lactone complexes, *endo*-**3** and *exo*-**7**, obtained in 64% overall yield and in a ratio of *ca.* 3 : 1, respectively.

Reduction of the side-chain carbonyl group of the inseparable iron complexes **3** and **7** was achieved in 71% yield using triisobutylaluminium to give **8** and **9**. NOE experiments performed on the mixture of **3** and **7** revealed that both existed exclusively in the *S-cis*-conformation as strong enhancements were observed between the protons α to the ketone and only the terminal protons of the allyl system. This strongly suggests the newly created stereocentres in **8** and **9** have the (*S*)-and (*R*)-configuration, respectively. Compounds **8** and **9**, which were



Scheme 1 *Reagents and conditions*: i, D-diethyl tartrate (18 mol%), $Ti(OPr^i)_4$ (15 mol%), Bu^tOOH (2 equiv.), 4 Å molecular sieves, CH_2Cl_2, −20 °C, 90 min, 70%; ii, CrO_3 (8.6 equiv.), pyridine (17.4 equiv.), CH_2Cl_2, 40 min, 85%; iii, $(EtO)_2P(O)CH_2CO(CH_2)_8OTBDPS$ **5** (1.2 equiv.), KHMDS (1.1 equiv.), THF, −78 °C, 50 min, 66%; iv, $Fe_2(CO)_9$ (2.1 equiv.), THF, 3 h, 64% (**3**:**7** = *ca.* 3 : 1); v, $AlBu^i_3$ (2.3 equiv.), benzene–toluene (4 : 1), 0 °C, 35 min, 53% **8**, 18% **9**; vi, $Ba(OH)_2$, MeOH, 5 min, 78%; vii, HF·py, THF, 18 h, 92%; viii, H_2O_2, NaOH, MeOH, 0 °C, 25 min, 94%; ix, $RuCl_2(PPh_3)_3$ (1 equiv.), benzene, 22 h, 73%; x, NaOCl (8 equiv.), KH_2PO_4 (23 equiv.), 2-methylbut-2-ene (45 equiv.), Bu^tOH–H_2O (1 : 1), 1 h; then CH_2N_2, 10 min, 49% (over 2 steps); xi, LiOH (6 equiv.), DME–H_2O (3 : 1), 3 h, 85%





the sole reduction products as determined by ^{1}H NMR and HPLC analysis, were readily separable by HPLC chromatography. Comparison of the ^{1}H NMR of the derived Mosher esters with the racemates indicated both **8** and **9** to have an e.e. >95%.

With **8** in hand we were able to proceed to the target molecule (Scheme 1). Treatment of **8** with barium hydroxide[12] resulted in a highly stereoselective decarboxylation to afford the η^4 diene-tricarbonyliron complex **10**, as a single diastereoisomer. The nature of the diene unit was confirmed as being (*E*,*E*) by the coupling constants between the vinylic protons, 8.0 and 5.0 Hz, being consistent with previously reported examples.[13] Removal of the silyl protecting group followed by decomplexation using methanolic hydrogen peroxide–sodium hydroxide[14] occurred smoothly to provide the free dienyllic diol **12**. In order to attain the correct level of oxidation required for the natural product, an approach involving stepwise oxidation of the primary hydroxy group proved to be the most beneficial. Thus, selective oxidation of the primary alcohol in **12** to the aldehyde **13** using dichlorotris(triphenylphosphine)ruthenium[15] was followed by treatment with buffered sodium chlorite in the presence of the radical scavenger, 2-methylbut-2-ene[16] to give the crude acid. In order to assist purification this crude acid was treated with diazomethane to afford the methyl ester **14**. Following purification by flash column chromatography, hydrolysis of **14** using lithium hydroxide in DME–water gave **1**‡ which was identical in all respects with that reported in the literature.[17]

This short, highly stereoselective synthesis of β-dimorphecolic acid clearly demonstrates the utility of carbonyl substituted π-allyltricarbonyliron lactone complexes in organic synthesis. Thus, we were able to use the tricarbonyliron tether to exert control over two distinct elements of stereochemistry, namely a 1,5-asymmetric induction to form the required stereogenic centre followed by a stereoselective decarboxylation reaction to control the (*E*,*E*)-geometry of the diene unit.

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Footnotes

† Compound **5** was prepared by alkylation of the dianion of diethyl (2-oxopropyl)phosphonate (NaH, BuLi, 0 °C) with $Br(CH_2)_7OTBDPS$, prepared by protection of the free alcohol (TBDPSCl, CH_2Cl_2, Et_3N, DMAP, 66% over 2 steps).

‡ Selected data for **1**: mp 38–40 °C (lit.,[17] 37–38 °C); $[\alpha]_D^{24}$ = +15.4 (*c* 1.0, MeOH) (lit.,[17] $[\alpha]_D^{24}$ = +15.2 (*c* 5.0, MeOH)]; ν_{max} (KBr)/cm^{-1} 3422 (OH), 2925, 2870, 1712–1458 (C=O, C=C), 1321, 1211 and 986; ^{1}H NMR δ (500 MHz, CD_3OD) 0.89 (3 H, t, *J* = 6.8 Hz, 18-H × 3), 1.23–1.61 (18 H, 3-H × 2, 4-H × 2, 5-H × 2, 6-H × 2, 7-H × 2, 8-H × 2, 15-H × 2, 16-H × 2, 17-H × 2), 2.06 (2 H, apparent q, *J* = 7.1 Hz, 14-H × 2), 2.21 (2 H, t, *J* 7.5 = Hz, 1-H × 2), 4.00 (1 H, apparent q, *J* = 6.6., Hz, 9-H), 5.51 (1 H, dd, *J* = 15.1, 6.6 Hz, 10-H), 5.66 (1 H, dt, *J* = 15.1, 7.1 Hz, 13-H), 6.02 (1 H, dd, *J* = 15.1, 10.5 Hz, 12-H) and 6.14 (1 H, dd, *J* = 15.1, 10.5 Hz, 11-H).

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