Stereoselective synthesis of 2-dienyl-substituted piperidines using an η^4-dienetricarbonyliron complex as the stereocontrolling element in a double reductive amination cascade†

Iwan Williams,[a] Keith Reeves,[b] Benson M. Kariuki[a] and Liam R. Cox*[a]

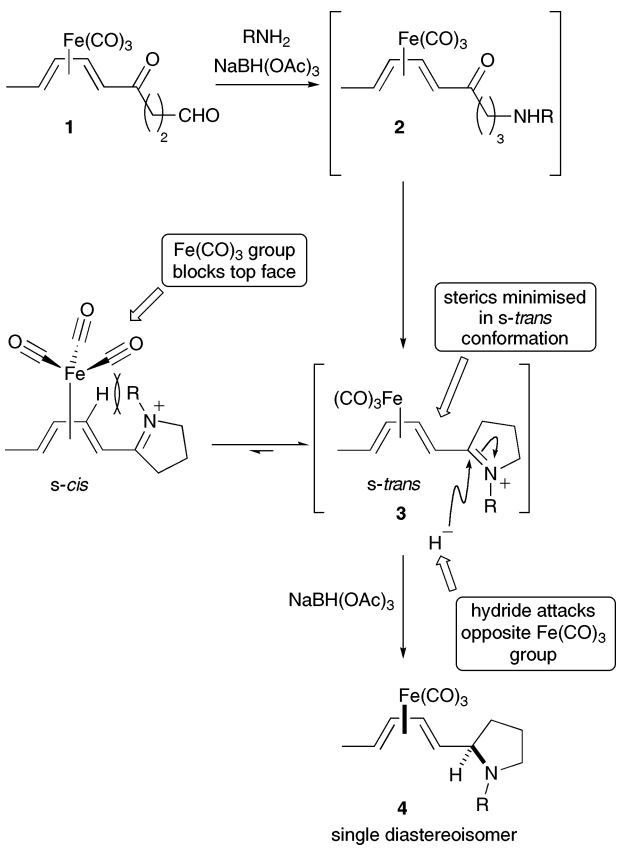
Received 16th July 2007, Accepted 31st August 2007
First published as an Advance Article on the web 12th September 2007
DOI: 10.1039/b710898b

In the presence of $NaBH(OAc)_3$, a 1,5-keto-aldehyde, contained within a side-chain of an η^4-dienetricarbonyliron complex, undergoes a double reductive amination sequence with a series of primary amines, to provide the corresponding piperidine products in good to excellent yield. The dienetricarbonyliron complex functions as a powerful chiral auxiliary in this cascade process, exerting complete control over the stereoselectivity of the reaction, with the formation of a single diastereoisomeric product. The sense of stereoinduction has been confirmed by X-ray crystallography. Removal of the tricarbonyliron moiety can be effected with $CuCl_2$ to afford the corresponding 2-dienyl-substituted piperidine in excellent yield. Attempted extension of this cyclisation strategy to the corresponding azepane ring system using a 1,6-keto-aldehyde as the cyclisation precursor was unsuccessful; in this case, the reaction stopped after a single reductive amination on the aldehyde to provide an acyclic keto-amine product.

Introduction

Unsymmetrically substituted η^4-dienetricarbonyliron complexes exhibit planar chirality and are readily prepared in enantiomerically pure form.[1] As a consequence, this class of organometallic compound has found widespread application as a chiral auxiliary in stereoselective synthesis.[1] The sterically demanding tricarbonyliron moiety in these (and related[2]) complexes serves to control the approach trajectory of external reagents on functionality appended to the diene ligand. Invariably, the external reagent attacks the face of the pendant functional group, which is remote from the bulky tricarbonyliron unit. Providing the functional group adopts a single reactive conformation, levels of diastereoselectivity in these addition reactions can be essentially complete. The reaction of nucleophiles with pendant ketone functionality in η^4-diene[3] and related π-allyltricarbonyliron lactone complexes[4] provides the paradigm in this area.

We recently extended the utility of this organometallic chiral auxiliary to the synthesis of 2-dienyl-substituted pyrrolidines, using a double reductive amination cascade to assemble the *N*-heterocycle (Scheme 1).[5] Thus, starting from keto-aldehyde complex **1**, a first reductive amination involving the more electrophilic aldehyde and a primary amine served to introduce a secondary amine into the pendant chain. Without isolating this intermediate, condensation of the secondary amine in **2** with the proximal ketone afforded a new iminium species **3**, which underwent reduction to generate the pyrrolidine product **4** as a single diastereoisomer (Scheme 1). Whilst a minor by-product in these reactions was the corresponding pyrrole, formed *via* a Paal–Knorr-type condensation,[6] this side-reaction could be minimised



Scheme 1 A stereoselective double reductive amination route to pyrrolidines.

[a]*School of Chemistry, University of Birmingham, Edgbaston, Birmingham, UK B15 2TT. E-mail: l.r.cox@bham.ac.uk; Fax: +44 (0)121 414 4403; Tel: +44 (0)121 414 3524*
[b]*Sandwich Laboratories, Pfizer Limited, Sandwich, Kent, UK CT13 9NJ*

† Electronic supplementary information (ESI) available: Experimental procedures and characterisation data for all compounds; ^{1}H-NMR and ^{13}C-NMR spectra for all compounds. See DOI: 10.1039/b710898b

by carrying out the reductive amination in the absence of a Brønsted acid.

The dienetricarbonyliron unit plays a dual role in this pyrrolidine synthesis: first, it ensures the intermediate cyclic iminium ion **3** adopts a single reactive conformation, which in this case, is the s-*trans* conformation, as this orientation minimises steric interactions between the diene ligand and nitrogen substituents in the pendant iminium ion **3**; second, the sterically demanding tricarbonyliron moiety ensures the external hydride source[7] reduces the cyclic intermediate by approaching *anti* to this large group.[8] Buoyed by the success of these reactions, we postulated that this methodology could be extended to the synthesis of larger *N*-heterocycles, in particular to 2-dienyl-substituted piperidines, which occur as structural motifs in a range of natural products including the cytotoxic piperidine alkaloid pseudodistomin C, **5**,[9] and the potent fish-feeding-deterrent corydendramine B, **6** (Fig. 1).[10] We now report in full how this double reductive amination methodology can indeed be extended to a highly stereoselective synthesis of 2-dienyl-substituted piperidines, but not to similarly substituted azepanes.

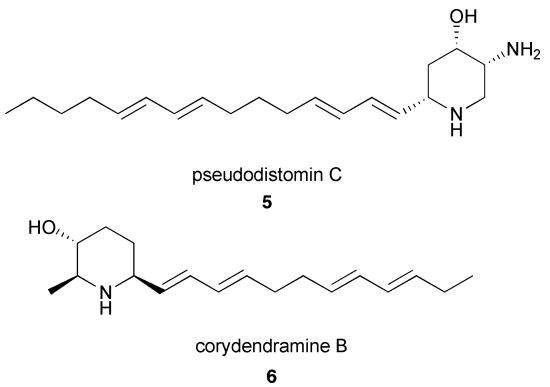
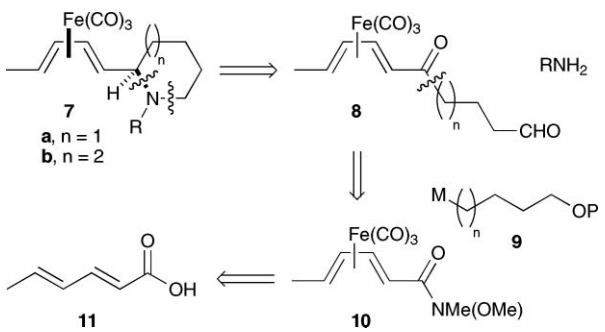


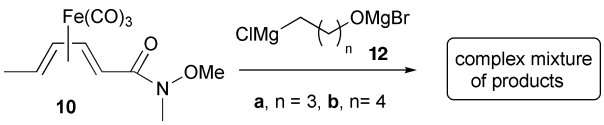
Fig. 1 Natural products possessing a 2-dienyl piperidine structural motif.

Our retrosynthetic analysis for these two classes of *N*-heterocycle is collectively outlined in Scheme 2. In analogy with our previous route to 2-dienyl-substituted pyrrolidines, we wished to construct the ring in **7** *via* a double reductive amination of the corresponding keto-aldehyde precursor **8**. We envisaged this cyclisation precursor could be accessed by addition of a suitably functionalised nucleophile **9** into Weinreb amide complex **10**, which is readily accessed from sorbic acid **11**.[5]



Scheme 2 Retrosynthetic analysis.

Our first targets were therefore the two cyclisation precursors, namely 1,5-keto-aldehyde **8a**, and 1,6-keto-aldehyde **8b**. A particularly direct route to these two cyclisation precursors would involve ketone formation by reaction of the Grignard reagents derived from commercially available 4-chlorobutan-1-ol and 5-chloropentan-1-ol, with Weinreb amide **10**, followed by oxidation of the resultant keto-alcohols. We first investigated the use of Grignard reagents prepared from these bifunctional starting materials without prior masking of the alcohol functionality. Using Normant's temporary protection strategy,[11] 4-chlorobutan-1-ol was treated with one equivalent of methylmagnesium chloride to generate the corresponding magnesium alkoxide, and then with magnesium metal to afford the desired Grignard reagent **12a**.[12] Unfortunately, reaction of **12a** with Weinreb amide **10** failed to afford the desired keto-alcohol; a complex mixture of products was obtained (Scheme 3). Similar results were obtained with the Grignard reagent, **12b**,[12] generated from 5-chloropentan-1-ol, which would have allowed us entry into the cyclisation precursor required for azepane synthesis.



Scheme 3 Treatment of Weinreb amide **10** with two Normant Grignard reagents failed to yield the desired hydroxy-ketone products.

Since we had previously used this type of alkoxy-substituted Grignard very effectively to access the 1,4-keto-aldehyde required for our pyrrolidine synthesis, we were disappointed by these results and tentatively postulate that the increased chain-length affects the aggregation state, and therefore the reactivity of these reagents; unfortunately the inclusion of TMEDA, which we hoped might disrupt (or at least modify) the aggregation state, failed to improve matters and we consequently resorted to protecting the alcohol functionality prior to Grignard formation. Focusing on the piperidine cyclisation precursor, our attention turned to the Grignard reagent **13**, derived from the corresponding THP-protected chloroalcohol, which was readily prepared under standard conditions from 4-chlorobutan-1-ol and dihydropyran in the presence of CSA. Unfortunately, reaction of **13**[13] with Weinreb amide **10** once again failed to provide the desired ketone product. A mixture of products was again formed in which the principal component was now secondary amide **15**, whose structure was confirmed by X-ray crystallography (Fig. 2)‡. The Grignard reagent **14**, in which the THP-ether protecting group had been

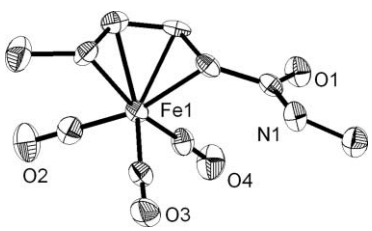
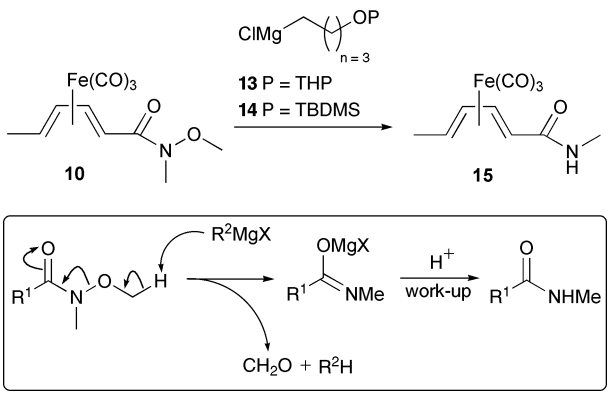


Fig. 2 ORTEP plot of **15**. Atomic displacement parameters at 293 K are drawn at the 30% probability level.

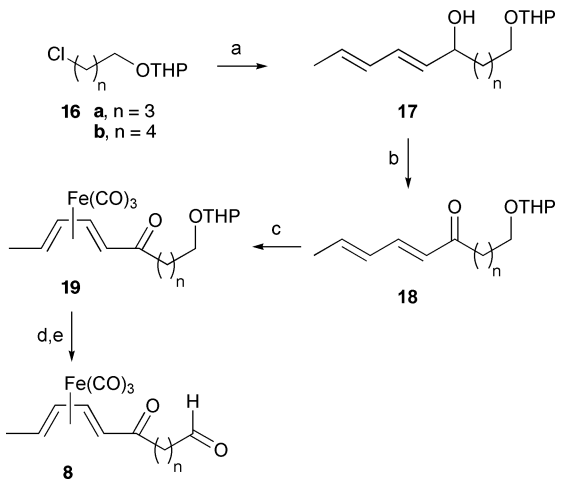
‡ CCDC reference numbers 654317 and 656908. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b710898b

exchanged for a TBDMS ether, gave similar results. The generation of a secondary amide product was unexpected, although is not without precedent; its formation can be attributed to the nucleophile acting preferentially as a base and leading to cleavage of the methoxy group in the Weinreb amide (Scheme 4).[14] This process can proceed through a number of mechanisms, although in the absence of an enolisable proton, as is the case with amide **10**, the reaction is thought to proceed *via* deprotonation of the methoxy group on the amide and subsequent elimination of formaldehyde, yielding the secondary amide on work-up (Scheme 4).[15]



Scheme 4 Addition of Grignard species **13** and **14** into Weinreb amide **10** provided a secondary amide rather than the desired ketone product.

Since we have successfully used a range of Grignard reagents to generate ketones from Weinreb amide **10**, its reactivity pattern with this set of functionalised organomagnesium reagents was surprising and we do not have an explanation for this change in selectivity. We briefly considered changing the oxidation state of the electrophile, and using a sorbaldehyde complex in place of Weinreb amide **10**, as the desired keto-aldehyde functionality could potentially be introduced simultaneously by oxidising the two alcohol functionalities that would result from the addition reaction. However, our own (and other groups') experience with oxidising alcohols α-to the diene ligand of tricarbonyliron complexes has revealed this to be a very difficult transformation to perform. All standard oxidants fail and 1,1′-(azodicarbonyl)dipiperidine, which has been used successfully by Pearson to effect this transformation,[16] is expensive. Anticipating problems with this approach further along the synthesis, we instead elected to introduce the side-chain prior to iron complexation. Thus, treatment of sorbaldehyde with the Grignard reagent derived from chloride **16a** yielded the 1,2-addition product, **17a**, as an inconsequential mixture of diastereoisomers in excellent yield. Oxidation of the dienylic alcohol in **17a** with MnO_2 furnished the corresponding dienone **18a**. Electron-deficient dienes of this type are generally good substrates for tricarbonyliron complexation; indeed, reaction of dienone **18a** with diironnonacarbonyl in THF afforded the ketone complex **19a** as a mixture of THP-diastereoisomers in good yield.[17] Elaboration to our desired 1,5-keto-aldehyde **8a** was now straightforward: deprotection of the THP group, followed by Swern oxidation of the resulting alcohol delivered the desired cyclisation precursor in good yield. The 1,6-keto-aldehyde precursor **8b** was obtained *via* the same synthetic pathway, only this time, starting from the THP ether of 5-chloropentan-1-ol **16b** (Scheme 5).

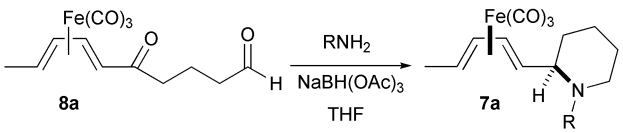


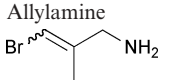
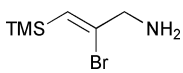
Scheme 5 Synthesis of the cyclisation precursors: *Reagents and conditions*: (a) Mg, $BrCH_2CH_2Br$, THF, 70 °C, then sorbaldehyde, **17a**, 98%; **17b**, 90%; (b) MnO_2, CH_2Cl_2, **18a**, 94%; **18b**, 91%; (c) $[Fe_2(CO)_9]$, Et_2O, 40 °C, **19a**, 71%; **19b**, 64%; (d) *p*PTS, EtOH, 50 °C, $n = 1$, 84%; $n = 2$, 93%; (e) Swern oxidation, **8a**, 77%, **8b**, 86%.

With our cyclisation precursors in hand, we were pleased to observe that treatment of 1,5-keto-aldehyde **8a** with a range of primary amines and $NaBH(OAc)_3$ in THF, under our optimised conditions for pyrrolidine synthesis,[5] effected the desired cascade reaction. Furthermore, since competing aromatisation side-reactions, which had sometimes attenuated the yield of our pyrrolidine products, were no longer an issue with these one-carbon-homologated substrates, all the piperidines, **7aa–7ag**, were isolated in good to excellent yield, and in every case as a single diastereoisomer as evidenced by analysis of the crude reaction mixture by ^{1}H-NMR (Table 1).

Crystals of piperidine (***E***)-**7af** suitable for analysis by X-ray diffraction allowed us to confirm the diastereoselectivity of the cyclisation reaction (Fig. 3)‡. The relative stereochemistry between the newly generated stereocentre and the planar chirality of

Table 1 Piperidine synthesis



Piperidine product	RNH_2	Isolated yield (%)
7aa	$BnNH_2$	85
7ab	*p*-$MeOPhCH_2NH_2$	82
7ac	$BuNH_2$	81
7ad	$HOCH_2CH_2NH_2$	71[a,b]
7ae	Allylamine	80
7af		86
7ag		73

[a] AcOH used to reduce the reaction pH to ~6. [b] Isolated % yield of the TBDMS-protected product (2 steps).

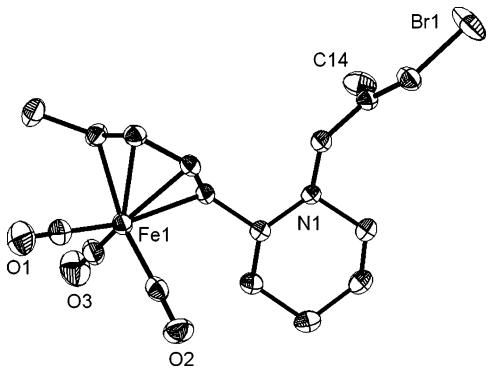
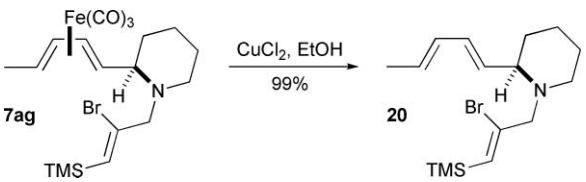


Fig. 3 ORTEP plot of piperidine (*E*)-**7af**. Atomic displacement parameters at 293 K are drawn at the 30% probability level.

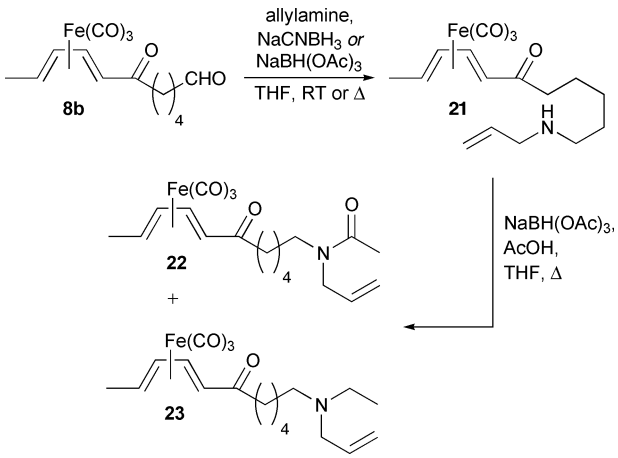
the iron complex is consistent with our working model, which features the hydride reducing agent approaching the s-*trans* conformer of the cyclic iminium species *anti* to the stereodirecting tricarbonyliron group.

Decomplexation of iron complexes can be effected in a variety of ways. Whilst our favoured approach employs basic peroxide,[18] this was not possible with vinyl bromide **7ag** owing to competing elimination of HBr leading to the corresponding acetylene. However, Cu(II)-mediated oxidative decomplexation proved equally effective, affording piperidine **20** in 99% yield (Scheme 6).[19]



Scheme 6 Oxidative decomplexation reveals a 2-dienyl-substituted piperidine product.

Having successfully extended the scope of our double reductive amination route to 2-dienyl-substituted piperidines, we were keen to see whether the strategy could also be used to access the corresponding azepane systems. The desired keto-aldehyde cyclisation precursor **8b** was synthesised as outlined above in Scheme 5. Unfortunately all attempts to generate the azepane ring system proved futile. Analysis of the crude reaction mixture resulting from reaction of 1,6-keto-aldehyde **8b** with allylamine and $NaBH(OAc)_3$ in THF, revealed the major product to be the secondary amine intermediate **21**. Thus reaction had apparently stopped after the first reductive amination step. Azepanes are known to be difficult substrates to form *via* reductive amination,[20] and even carrying out the reaction at elevated temperature failed to encourage cyclisation. Since Brønsted acids are commonly employed in reductive amination reactions to increase the rate of iminium ion formation,[21] a solution of secondary amine **21** in THF was heated under reflux in the presence of two equivalents of $NaBH(OAc)_3$ and one equivalent of acetic acid in an effort to drive the cyclisation. However, whilst these reaction conditions now resulted in complete consumption of the secondary amine starting material, they once again failed to effect cyclisation; instead the presence of the acetic acid simply resulted in the formation of the acetylated product **22**, and tertiary amine **23**.[22] Repeating the reaction with $NaCNBH_3$ as the reducing agent,[21b] again at elevated temperature, failed to improve matters; the only product obtained was once more the secondary amine **21** (Scheme 7).



Scheme 7 Attempted azepane synthesis afforded products arising from a single reductive amination.

In summary, we have successfully extended the scope of our double reductive amination strategy to the synthesis of 2-dienyl-substituted piperidines. These reactions proceed in very good yield and with complete diastereoselectivity. The stereochemical outcome has been confirmed by X-ray crystallography and supports our working model in which the intermediate cyclic iminium species is reduced in its s-*trans* conformation with hydride attack proceeding *anti* to the tricarbonyliron group. Attempts to extend this approach to the azepane framework have not proved fruitful, yielding, at best, the keto-amine intermediate **21**, which demonstrates the current limitation of the method. The 2-dienyl-substituted piperidine products are ripe for further elaboration. Future work will focus on using the diene functionality to access bicyclic indolizidine and quinolizidine frameworks, which are common structural motifs in natural product chemistry.

Experimental procedure for piperidine synthesis

[(2*Z*,1*S,4*S**,2′*R**)-1-[(*N*-Benzyl)piperidin-2′-yl]-(1,2,3,4-η)-penta-2-en-1,4-diyl]tricarbonyliron 7aa.** A solution of keto-aldehyde **8a** (57 mg, 0.186 mmol) in THF (1 mL) was added to a stirred suspension of $BnNH_2$ (24 μL, 0.223 mmol) and $NaBH(OAc)_3$ (158 mg, 0.744 mmol) in THF (2 mL). The reaction mixture was stirred at rt for 12 h, and then partitioned between Et_2O (5 mL) and $NaHCO_3$ solution (5 mL). The aqueous phase was extracted with Et_2O (3 × 5 mL), and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification of the residue by SiO_2 column chromatography (hexane–Et_2O, 6 : 1 plus 1% Et_3N) yielded piperidine **7aa** as a yellow oil (60 mg, 85%); R_f (hexane–Et_2O, 4 : 1) 0.44; (Found: C, 63.23; H, 5.93; N, 3.79. $C_{20}H_{23}FeNO_3$ requires C, 63.01; H, 6.08; N, 3.67%); υ_{max}(film)/cm^{-1} 3027 w, 2934 s, 2856 m, 2788 m, 2039 s (CO), 1962 s br (CO), 1494 w, 1442 m, 1380 w, 1366 w, 1029 w; δ_H(300 MHz; $CDCl_3$) 1.05–1.17 (1H, m, C(1)*H*), 1.31–1.55 (6H, stack, including [1.40 (3H, d, *J* 6.3, C(5)H_3], C(4)*H*, CH_2CH$_2$CHN, C(5)H_3), 1.58–1.78 (3H, stack, CH_aH$_b$CHN, CH_2CH$_2$N), 1.83–2.08 (3H, stack,

CH_aH_bCHN, CH_aH_bN), 2.60–2.74 (1H, m, CH_aH_bN), 3.06–3.21 (1H, m, CH_aH_bPh), 4.20–4.37 (1H, m, CH_aH_bPh), 4.98 (1H, dd, *J* 8.5, 4.8, C(2)*H* or C(3)*H*), 5.03–5.13 (1H, m, C(3)*H* or C(2)*H*), 7.17–7.39 (5H, stack, Ph*H*); δ_C(100 MHz; $CDCl_3$) 18.8 (CH_3, *C*5), 23.3 (CH_2, CH_2CH_2CHN), 25.2 (CH_2, CH_2CH_2N), 35.6 (CH_2, CH_2CHN), 50.7 (CH_2, CH_2N), 58.0 (CH, *C*4), 58.8 (CH_2, CH_2Ph), 65.2 (2 × CH, *C*1, *C*HN, overlapping resonances), 84.2 (CH, *C*3), 84.5 (CH, *C*2), 127.0 (CH, *p*-Ph), 128.5 (CH, *m*-Ph), 129.0 (CH, *o*-Ph), (C_{quat}, *ipso*-Ph) not observed; *m*/*z* (ES) 382.0 [$(M + H)^+$, 98%], 298.0 (100, M + H-3CO) [Found $[M + H]^+$ 382.1116. $C_{20}H_{24}FeNO_3$ requires M + H, 382.1106].

Acknowledgements

We are grateful to Pfizer for an industrial CASE studentship to I. W.

References

1 For reviews, see: (*a*) H.-J. Knölker, *Curr. Org. Synth.*, 2004, **1**, 309–331; (*b*) W. A. Donaldson, *Curr. Org. Chem.*, 2000, **4**, 837–868; (*c*) H.-J. Knölker, *Chem. Rev.*, 2000, **100**, 2941–2961; (*d*) H.-J. Knölker, *Chem. Soc. Rev.*, 1999, **28**, 151–157; (*e*) L. R. Cox and S. V. Ley, *Chem. Soc. Rev.*, 1998, **27**, 301–314; (*f*) C. Iwata and Y. Takemoto, *Chem. Commun.*, 1996, 2497–2504.
2 π-Allyltricarbonyliron lactone complexes behave similarly: S. V. Ley, L. R. Cox and G. Meek, *Chem. Rev.*, 1996, **96**, 423–442.
3 (*a*) M. Franck-Neumann, P. Chemla and D. Martina, *Synlett*, 1990, 641–642; (*b*) N. A. Clinton and C. P. Lillya, *J. Am. Chem. Soc.*, 1970, **92**, 3058–3064.
4 (*a*) S. V. Ley, L. R. Cox, G. Meek, K.-H. Metten, C. Piqué and J. M. Worrall, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3299–3313; (*b*) S. V. Ley and L. R. Cox, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3315–3325.
5 I. Williams, B. M. Kariuki, K. Reeves and L. R. Cox, *Org. Lett.*, 2006, **8**, 4389–4392.
6 L. Knorr, *Chem. Ber.*, 1884, **17**, 1635.
7 $NaCNBH_3$ and $NaBH(OAc)_3$ were similarly effective.
8 For a related reaction that also proceeds through an s-*trans* conformation: Y. Takemoto, J. Takeuchi, E. Matsui and C. Iwata, *Chem. Pharm. Bull.*, 1996, **44**, 948–955.
9 Y. Doi, M. Ishibashi and J. Kobayashi, *Tetrahedron*, 1996, **52**, 4573–4580.
10 N. Lindquist, N. Shigematsu and L. Pannell, *J. Nat. Prod.*, 2000, **63**, 1290–1291.
11 G. Cahiez, A. Alexakis and J. F. Normant, *Tetrahedron Lett.*, 1978, **19**, 3013–3014.
12 L. F. Tietze, H. Schirok and M. Wöhrmann, *Chem.–Eur. J.*, 2000, **6**, 510–518.
13 T. Harada, E. Akiba and A. Oku, *Tetrahedron Lett.*, 1985, **26**, 651–654.
14 (*a*) O. Labeeuw, D. Blanc, P. Phansavath, V. Ratovelomanana-Vidal and J.-P. Genêt, *Eur. J. Org. Chem.*, 2004, 2352–2358; (*b*) G. L. Mislin, A. Burger and M. A. Abdallah, *Tetrahedron*, 2004, **60**, 12139–12145.
15 S. L. Graham and T. H. Scholz, *Tetrahedron Lett.*, 1990, **31**, 6269–6272.
16 A. J. Pearson and A. Alimardanov, *Organometallics*, 1998, **17**, 3739–3746.
17 Sorbaldehyde is supplied as a 95 : 5 (*E*–*E*) : (*E*–*Z*) mixture of isomers. As a result, trace impurities were carried through both the Grignard addition and allylic oxidation reactions. However, during the tricarbonyliron complexation reaction, the mixture of diene stereoisomers converged on a single (*E*,*E*)-diene complex. Here, double bond isomerisation reactions are probably proceeding *via* η^3-iron hydride species. T. A. Manuel, *J. Org. Chem.*, 1962, **27**, 3941–3945.
18 M. Franck-Neumann, M. P. Heitz and D. Martina, *Tetrahedron Lett.*, 1983, **24**, 1615–1616.
19 D. J. Thompson, *J. Organomet. Chem.*, 1976, **108**, 381–383.
20 D. M. Laventine, P. R. Jenkins and P. M. Cullis, *Tetrahedron Lett.*, 2005, **46**, 2295–2298.
21 (*a*) A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff and R. D. Shah, *J. Org. Chem.*, 1996, **61**, 3849–3862; (*b*) R. F. Borch, M. D. Bernstein and H. D. Durst, *J. Am. Chem. Soc.*, 1971, **93**, 2897–2904.
22 (*a*) G. W. Gribble, P. D. Lord, J. Skotnicki, S. E. Dietz, J. T. Eaton and J. L. Johnson, *J. Am. Chem. Soc.*, 1974, **96**, 7812–7814; (*b*) G. W. Gribble, J. M. Jasinski, J. T. Pellicone and J. A. Panetta, *Synthesis*, 1978, 766–768; (*c*) P. Marchini, G. Liso, A. Reho, F. Liberatore and F. M. Moracci, *J. Org. Chem.*, 1975, **40**, 3453–3456; (*d*) D. De, F. M. Krogstad, L. D. Byers and D. J. Krogstad, *J. Med. Chem.*, 1998, **41**, 4918–4926.