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Asymmetric synthesis of (1R,8S)- and (1S,8S)-1-Hydroxypyrrolizidin-3-ones *via* the aldol reaction between N-Boc-(S)-Prolinal and chiral acetate enolate equivalents derived from (S)- and (R)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_3$]

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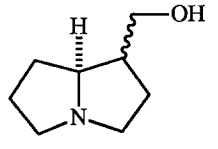
Abstract: Syntheses of both title compounds have been achieved with excellent stereocontrol using chiral acetate enolate equivalents derived from the iron acetyl complex [(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_3$]. The different diastereoselectivities in the two syntheses are rationalised in terms of the concept of double asymmetric induction and the transition state models for the aldol reactions of such enolates are discussed.

The pyrrolizidine alkaloids are an important class of plant-derived natural products, most of which are esters of 1-(hydroxymethyl)-pyrrolizidine **1**[1].



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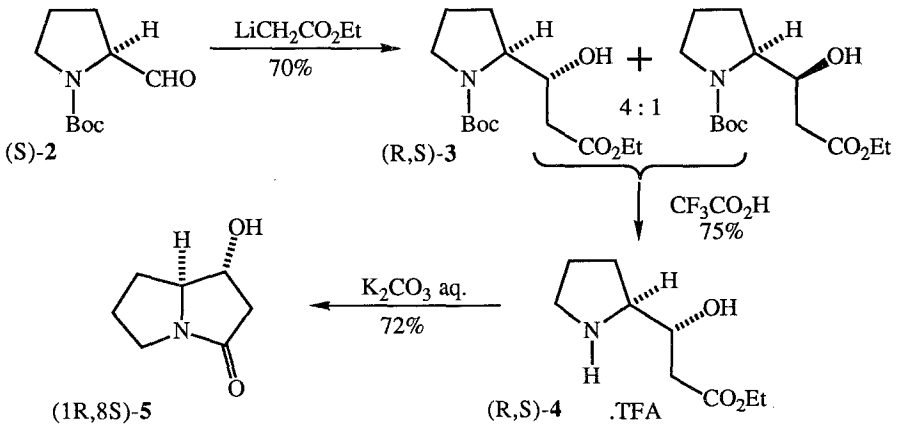
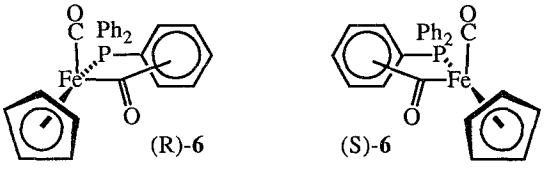
Whilst many of these compounds have acute cytotoxic effects, others exhibit more useful pharmacological properties as anti-tumour agents[2]. The stereoselective synthesis of such compounds is therefore of great interest and a number of synthetic approaches have been reported[3]. The synthesis of homologues where the hydroxymethyl group at C1 has been replaced by a hydroxyl group is also important for studies of structure-activity relationships and possible pharmaceutical application.

Recently Hanson *et al.* demonstrated that N-Boc-(S)-prolinal (S)-**2** undergoes a moderately diastereoselective reaction with the lithium enolate derived from ethyl acetate[4]. Although the ratio of (R,S)-**3** to its epimer was only 4:1, recrystallisation of intermediate (R,S)-**4** made it possible to prepare homochiral (1R,8S)-**5**. In the aldol reaction, attack by the enolate on the *Re* face of the aldehyde is preferred because of the effect of the neighbouring stereogenic centre. In this way, modest stereocontrol is exerted over the newly formed stereogenic centre, which eventually becomes C1 in the pyrrolizidinone (Scheme 1).

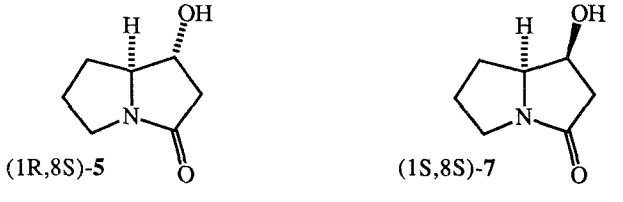


Scheme 1

We have already reported that the diethyl aluminium enolate derived from [(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_3$] **6** undergoes highly stereoselective (95:5 - >99:1) aldol reactions with achiral aldehydes[5] (the (R) enolate favours attack on the *si* face of the aldehyde and the (S) enolate the *re* face). Liebeskind has reported complementary aldol stereoselectivities for the corresponding tin (II) enolates, that is where the (R) enolate favours attack on the *re* face and the (S) enolate the *si* face, although the selectivities are somewhat lower (90:10 - 95:5).[6]

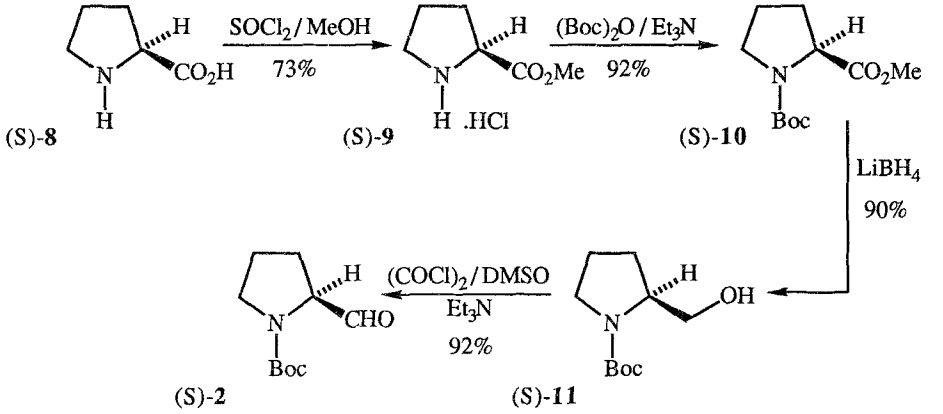


We describe here the double asymmetric induction in the aldol reaction between N-Boc-(S)-prolinal (S)-**2** and chiral acetate enolate equivalents derived from [(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_3$] **6** and its application to the asymmetric synthesis of (1R,8S)- and (1S,8S)-1-hydroxypyrrolizidin-3-ones (1R,8S)-**5** and (1S,8S)-**7**. Part of this work has been previously communicated[7].



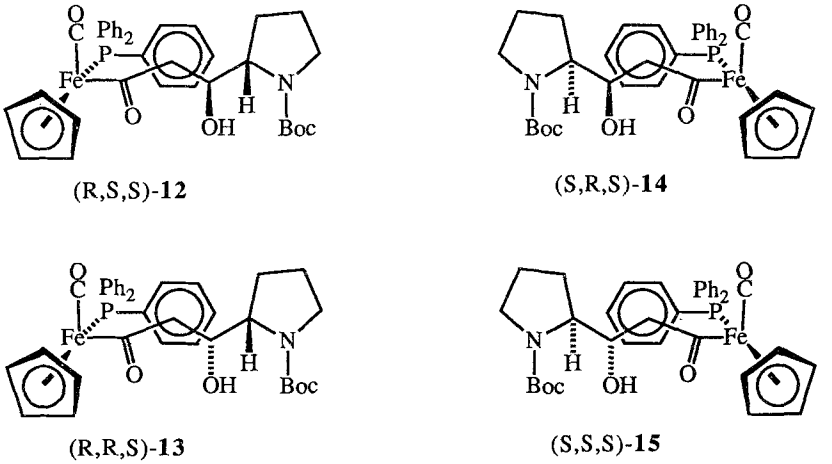
Results and Discussion

The homochiral aldehyde (S)-**2** was prepared in four steps from L-proline (S)-**8** according to the method of Harris *et al.*[8] This reduction-oxidation sequence is preferred to direct reduction of ester (S)-**10** with DIBAL in toluene[4,8], since the latter method gives a product contaminated with alcohol (S)-**11** even at low temperature (Scheme 2).



Scheme 2

The availability of both enantiomers of $(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)(COCH_3)$ **6** in homochiral form, together with the complementary stereoselectivity that may be obtained by transmetallating its enolates[5,6], should allow the synthesis of all four of the diastereoisomeric β-hydroxyacyl complexes **12-15** (Scheme 3) with the iron chiral auxiliary overpowering the inherent stereoselectivity of the aldehyde (the stereocentres are listed in the order; iron centre, β-hydroxy acyl centre and γ-amino centre).

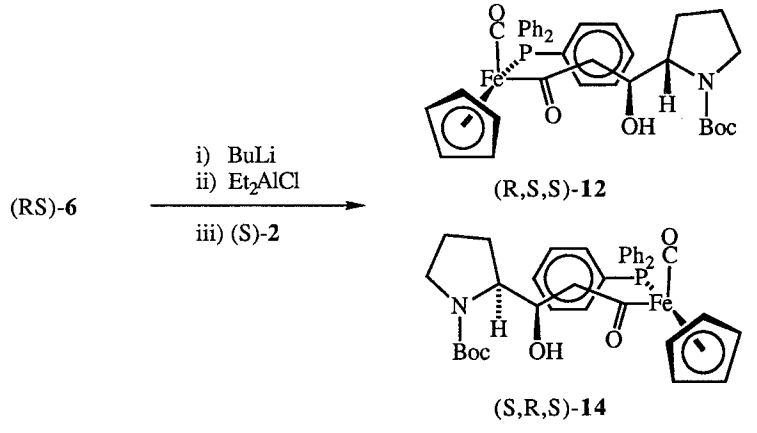


Scheme 3

In the formation of (1R,8S)-**5** and (1S,8S)-**7**, the (S) configuration at C8 is derived from the protected prolinal while that at C1 is determined by the asymmetric aldol reaction. Thus β-hydroxy acyl complexes **13** and **14** will lead to (1R,8S)-1-hydroxypyrrolizidin-3-one **5** whereas **12** and **15** will form the (1S,8S) diastereoisomer **7**. Furthermore, for the diethyl aluminium enolates it was expected that the formation of **14** over **15** would be more selective than the formation of **12** over **13** since the former case involves the matched combination with both the (S)-enolate and the stereogenic centre in the aldehyde favouring attack on the *re* face, while the latter case involves the mismatched combination. For similar reasons, with the tin enolates the formation of **13** over **12** should be more selective than **15** over **14**.

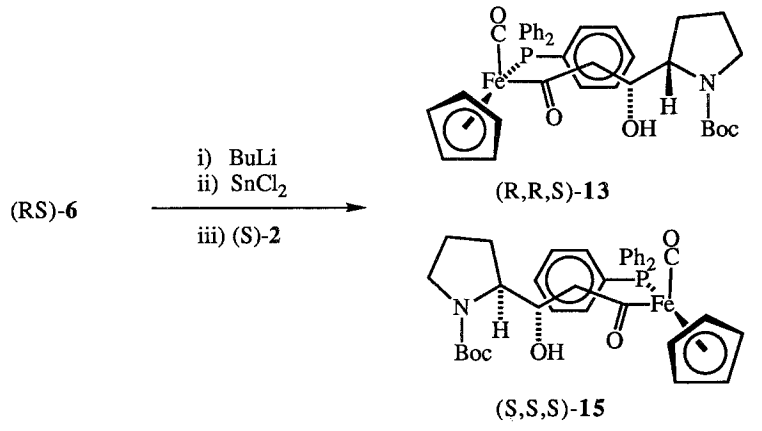
Previous studies have indicated that diethylaluminium enolates derived from (RS)-**6** generally show greater diastereoselectivities than do tin enolates but as both species promised routes to both (1R,8S)-**5** and (1S,8S)-**7**, it was decided to make a comparison on the basis of the reactions of racemic enolates.

Addition of one equivalent of (S)-N-Boc-prolinal (S)-**2** to a THF solution of the diethylaluminium enolate of (RS)-**6** at -100°C gave, after work-up, a 51:1.5:47:<0.5 mixture of the (R,S,S)-**12**, (R,R,S)-**13**, (S,R,S)-**14** and (S,S,S)-**15** diastereoisomers respectively. This product distribution is consistent with the overall concept of double asymmetric induction as described by Masamune[9], the aldehyde showing a diastereoselectivity of 75:25 (favouring attack on the *re* face) and the iron chiral auxiliary a selectivity of 99:1 (Scheme 4). Chromatography on alumina (grade V) gave two fractions; the less polar one containing the (S,R,S)-**14** diastereoisomer whilst the more polar fraction contained the three other diastereoisomers (R,S,S)-**12**, (R,R,S)-**13** and (S,R,S)-**14**.



Scheme 4

In contrast, addition of one equivalent of (S)-**2** to the tin (II) enolate of (RS)-**6** (formed from by transmetallation of the lithium enolate with tin (II) chloride at -40°C) gave, after work-up and chromatographic recovery of starting complex, a 1:51:7:41 mixture of the (R,S,S)-**12**, (R,R,S)-**13**, (S,R,S)-**14** and (S,S,S)-**15** diastereoisomers. This ratio indicates that the aldehyde shows a diastereoselectivity of 75:25 and the chiral auxiliary a selectivity of 95:5. Thus while the diastereofacial selectivity of the aldehyde is independent of the nature of the enolate, it is clear that the use of diethylaluminium enolates is preferable in this type of asymmetric process (Scheme 5).



Scheme 5

Table 1 Product ratios for the reactions of racemic enolates of complex (RS)-**6** with aldehyde (S)-**2**.

Enolate	Counterion	Aldehyde	Yield*	12	13	14	15
RS-**6**	$AlEt_2$	(S)-**2**	79%	51	1.5	47	<0.5
RS-**6**	Sn (II)	(S)-**2**	81%	1	51	7	41

* Based on recovered starting complex

The assignments shown above were made on the basis of the pyrrolizidine products obtained from the major products of the diethylaluminium enolate reactions (*vide infra*). In the past, assignments have been made on the basis of a comparison of ^{1}H n.m.r. data with that of compounds whose absolute configurations have been established by X-ray crystallography[6]. Generally, the diastereoisomer favoured by diethylaluminium enolates shows a smaller difference in chemical shift between the diastereotopic $COCH_2$ methylene protons than does the diastereoisomer favoured by tin enolates[10]. In the present series, however, this correlation is unreliable because of the influence of a third stereogenic centre (Table 2).

Table 2 Selected ^{1}H n.m.r. data for diastereoisomers **12-15**.

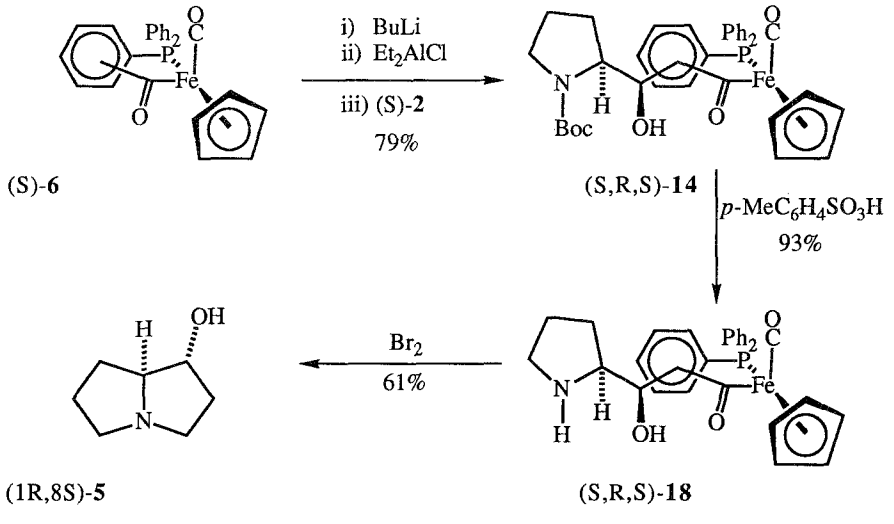
Configuration at Iron	R	R	S	S
Enolate Counterion	Et_2Al	Sn (II)	Et_2Al	Sn (II)
δ ($COCH_2$) / ppm	3.09	2.91	3.13	2.83
	2.56	2.42	2.58	2.53
δ (N-Boc) / ppm	1.40	1.42	1.41	1.43
Diastereoisomer	**12**	**13**	**14**	**15**

^{1}H n.m.r. spectra of the aldol product mixtures recorded in $CDCl_3$ at ambient temperature were broadened due to restricted rotation about the N-C bond of the carbamate. This effect was eliminated by obtaining spectra in d^6-DMSO at 360K, so that the signals due to the nine equivalent protons in the Boc groups of the four diastereoisomers appeared as sharp singlets in the region around $\delta = 1.40$. Diastereomer ratios quoted are based on integration of these signals.

Since greater selectivity was seen with the diethylaluminium enolate, it was decided to repeat this reaction with homochiral enolates. In analogous reactions, (R)-**6** gave a 97:3 mixture of the (R,S,S)-**12** and (R,R,S)-**13** diastereoisomers whereas (S)-**6** gave a >99:<1 mixture of the (S,R,S)-**14** and (S,S,S)-**15** diastereoisomers, entirely consistent with the earlier results. Spectroscopic analysis of the products obtained from these reactions allowed unambiguous assignment of the configurations of all four diastereoisomers **12-15**.

Attempts to cleave the Boc protecting group from mixtures of **12-15** with trifluoroacetic acid or trimethylsilyl iodide resulted in substantial decomposition of the organometallic complexes. However, treatment with *p*-toluenesulphonic acid in THF overnight gave the corresponding deprotected complexes **16-19** in good yield and decomplexation with bromine in dichloromethane solution afforded the desired products **5** and **7**.

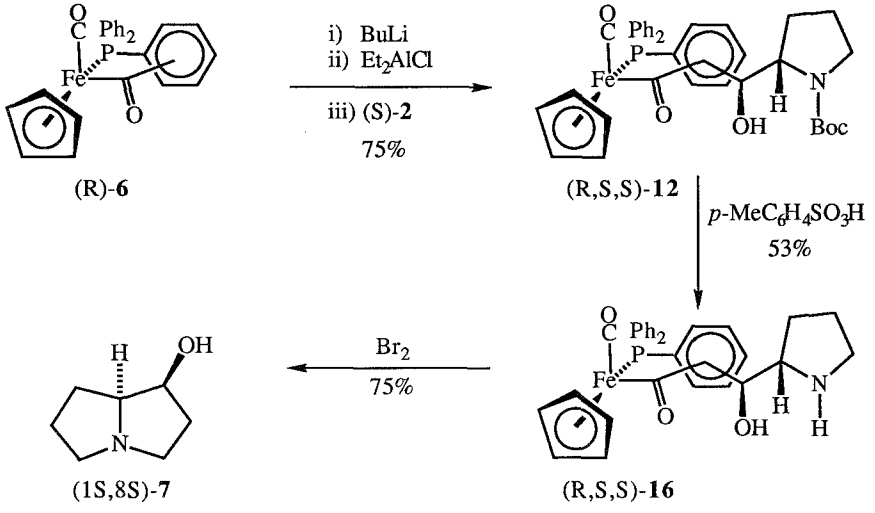
Deprotection and decomplexation of the β-hydroxyacyl complexes formed in the reactions of homochiral enolates gave products with the same diastereoisomeric purity as the starting materials indicating that there was no epimerisation under the deprotection/decomplexation conditions. Thus the single diastereoisomer (S,R,S)-**14** formed from the reaction of the (S) enantiomer of iron acyl complex (S)-**6** with N-Boc-(S)-prolinal (S)-**2** gave diastereoisomerically pure (1R,8S)-**5** directly, [m.p. 81-82°C, $[\alpha]^{20}_D$ - 97.0 (c = 0.3, $CHCl_3$): Lit.[4] m.p. 84-86°C, $[\alpha]^{20}_D$ -91.5 (c = 1.0, $CHCl_3$)] (Scheme 6).



Scheme 6

Similarly the 97:3 mixture of (R,S,S)-**12** and (R,R,S)-**13** diastereoisomers formed in the reaction between the diethylaluminium enolate derived from (R)-**6** and (S)-N-Boc-prolinal (S)-**2** was converted into a

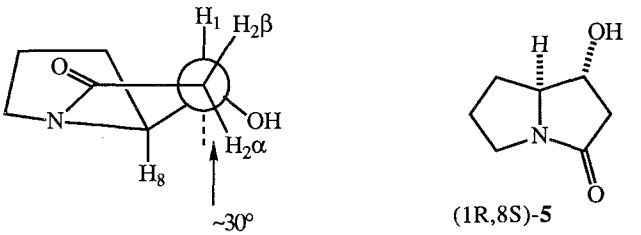
97:3 mixture of (1S,8S)-**7** and (1R,8S)-**5**. In this case a single recrystallisation gave diastereoisomerically pure (1S,8S)-**7** [m.p. 118-119°C, $[\alpha]^{20}_D$ -48.8 (c = 0.3, $CHCl_3$)] (Scheme 7).



Scheme 7

Further examination of the diastereoisomeric pyrrolizidinones (1R,8S)-**5** and (1S,8S)-**7** by 500 MHz ^1H n.m.r. spectroscopy revealed some unusual features which gave a clear indication of the lowest energy conformations for the molecules in solution. Initially all signals were assigned unambiguously by 2D ^1H-^1H correlation (COSY) experiments. In the (1R,8S) diastereoisomer **5** the protons at C2 (δ = 2.73) were apparently magnetically equivalent, showing no AB-type coupling, but the same coupling to H_1 ($J_{1,2\alpha} = J_{1,2\beta}$ = 8.2 Hz). This splitting was unchanged when d^6 benzene was used as solvent and indicates that the preferred conformation is that shown (Figure 1).

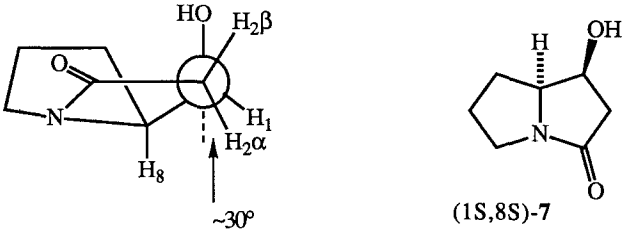
Figure 1 Newman Projection along the C2 - C1 axis in (1R,8S)-**5**.



In contrast the C2 protons in the (1S,8S) diastereoisomer **7** are magnetically very different (δ = 2.43, 2.98). The higher field proton ($H_{2\beta}$) appears as a simple doublet showing a large geminal coupling ($J_{2\alpha,2\beta}$ =

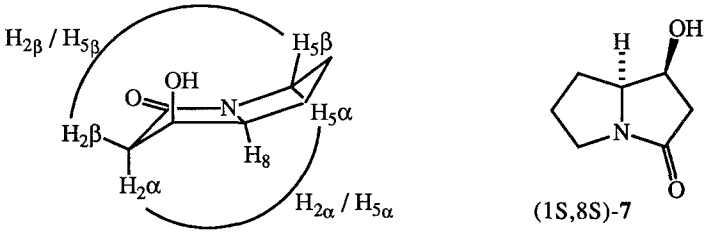
16.7 Hz) but no vicinal coupling to H_1, suggesting that the torsional angle between the two is approximately 90° (Figure 2).

Figure 2 Newman Projection along the C2 - C1 axis in (1S,8S)-**7**.



The lower field proton ($H_{2\alpha}$) appears as a doublet of doublets by virtue of the geminal coupling and the vicinal coupling to H_1 ($J_{1,2\alpha}$ = 4.9 Hz). However each line is further split into a triplet as a result of long range couplings to $H_{5\alpha}$ and $H_{5\beta}$ ($J_{2\alpha,5\alpha} = J_{2\alpha,5\beta}$ = 1.3 Hz). The latter assignments were supported by decoupling experiments (Figure 3).

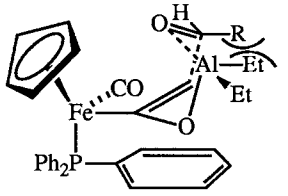
Figure 3 Long Range ^1H - ^1H n.m.r. Couplings in (1S,8S)-**7**.



Discussion

The synthesis of (1R,8S)-**5** and (1S,8S)-**7** from L-proline (S)-**8** with differing diastereoselectivities demonstrates the general principle of double asymmetric induction as described by Masamune[9]. Taking a value for the diastereofacial selectivity of the substrate electrophile of approximately 3:1 and a value of 100:1 for the iron chiral auxiliary, we can use Masamune's argument to calculate the expected diastereoselectivities with which the products ought to be formed. Both the >99:<1 selectivity for the (1R,8S) diastereoisomer **5** (calculated at >99:<1) and the 97:3 ratio for the (1S,8S) diastereoisomer **7** (calculated at 97:3) show remarkable agreement between theory and experiment. Although Masamune states that perfect agreement is only possible when there is no perturbation of the idealised transition states for the two reactive species, the examples given are restricted to acyclic compounds. In the work we have described, where the diastereofacial selectivity of L-proline (S)-**8** is not a function of an acyclic species, good agreement is still obtained. This implies that the transition state is such that the stereodirecting stereogenic centre of the proline derived residue does not perturb the idealised transition state for the chiral auxiliary.

The stereoselectivity of the reaction of diethylaluminium enolates of complex (RS)-**6** with achiral aldehydes has been explained previously[11] on the basis of a preferred "boat" transition state **21**. The corresponding "chair" transition states are disfavoured due to the necessity of placing one of the ethyl substituents on the aluminium counterion in an axial position proximate to the cyclopentadienyl ligand. The other "boat" transition state **20** is destabilised by a non-bonded interaction between the alkyl group of the aldehyde and an ethyl group on aluminium. In the favoured transition state **21** the stereogenic centre of the aldehyde does not interact with the stereogenic iron centre, and this may explain why the reaction does not depart from Masamune's principle (Scheme 8).



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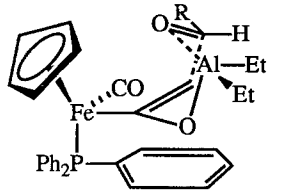

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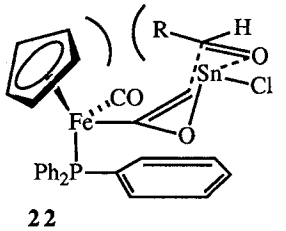
Scheme 8

Our results also demonstrate the highly desirable property of iron acyl chiral auxiliaries in showing complementary selectivity when the counterion is changed. It has been proposed that this reversal is due to there being a carbon-tin single bond which interacts with the carbon-oxygen bond of the aldehyde *via* a four-membered transition state[10]. We feel it is more likely that such a reaction will employ one of the "chair" transition states disfavoured for aluminium enolates. A tin (II) enolate with a lone pair and a single chlorine atom will not be forced to place a bulky group in an axial position and could react *via* **23** to give the observed product. The other "chair" transition state **22** is disfavoured due to repulsion between the alkyl sidechain of the aldehyde and the cyclopentadienyl ligand on iron (Scheme 9).



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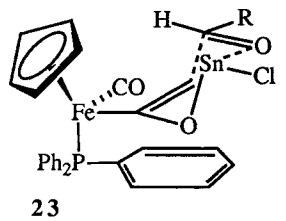

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Scheme 9

In conclusion, the iron chiral auxiliary allows ready access to both the (1R,8S) and (1S,8S) diastereoisomers of the target compound and provides both of these in homochiral form. The different stereoselectvities of these reactions may be rationalised by Masamune's theory of double asymmetric induction with the diastereoselectivity of the enolate overpowering that of the chiral electrophile.

Experimental

General - All manipulations of organometallic complexes were performed under an atmosphere of nitrogen with deoxygenated solvents and using standard vacuum line and Schlenk tube techniques[12]. Butyllithium was used as a 1.6M solution in hexanes and diethylaluminium chloride as a 2.0M solution in toluene. Tin (II) chloride was dried by stirring with acetic anhydride for 48 h, washing with sodium-dried ether and drying *in vacuo* for 120 h. Dimethyl sulphoxide and triethylamine were dried over 4Å molecular sieves prior to use. Tetrahydrofuran was dried over sodium benzophenone ketyl and distilled.

Melting points were determined using a Gallenkamp apparatus and are uncorrected. Optical rotations at the sodium D line were recorded on a Perkin-Elmer 241 polarimeter at 20°C. Elemental analyses were performed by the Dyson Perrins analytical department. Infra-red spectra were recorded in dichloromethane solution on Perkin-Elmer 297 and 781 spectrophotometers. ^{1}H n.m.r. spectra were recorded on Bruker WH300 (300.13 MHz) and AM500 (500.25 MHz) spectrometers whereas ^{13}C and ^{31}P n.m.r. spectra were recorded on a Bruker AM250 (^{13}C; 62.90 MHz. ^{31}P; 101.26 MHz) instrument. Spectra were recorded in $CDCl_3$ solution at ambient temperature unless otherwise specified. Mass spectra for organometallic complexes were obtained on a V.G. Micromass ZAB 1F instrument using field-desorption techniques whilst those for organic compounds were obtained on the same instrument using chemical ionisation methods.

Synthesis of N-Boc-(S)-prolinal (S)-**2** - N-Boc-(S)-proline methyl ester (S)-**10**, N-Boc-(S)-prolinol (S)-**11** and N-Boc-(S)-prolinal (S)-**2** were prepared according to the general method of Harris *et al.*[8], yields and spectroscopic data being shown below.

N-Boc-(S)-proline methyl ester (S)-**10** - Colourless oil (92%); $[\alpha]_D$ -56.5 (c = 4.2, $CHCl_3$), lit[8] $[\alpha]_D$ -54.37 (c = 3.67, $CHCl_3$); υ_{max} (film) 1750 (C=O, ester) and 1700 cm^{-1} (C=O, amide); δ_H (300 MHz, $CDCl_3$) (two rotamers, population 40:60) 4.30, 4.21 (1H, dd, **CH**N), 3.71 (3H, s, O**CH**$_3$), 3.68-3.35 (2H, m, **CH**$_2$N), 2.28-2.13, 2.01-1.79 (4H, m, **CH**$_2$**CH**$_2$CH$_2$N) and 1.45, 1.40 (9H, s, C(**CH**$_3$)$_3$); δ_H (300 MHz, d_6-DMSO, 360K, signals due to rotamers coalesce); δ_C (62.9 MHz, $CDCl_3$) 173.6, 173.4 (2s, **C**O$_2$CH$_3$), 154.3, 153.7 (2s, **C**O$_2$C(CH$_3$)$_3$), 79.7 (s, **C**(CH$_3$)$_3$), 59.0, 58.7 (2s, **CH**N), 51.8 (s, CO$_2$**CH**$_3$), 46.4, 46.2 (2s, **CH**$_2$N), 30.8, 29.8 (2s, **CH**$_2$CHN), 28.2 (s, C(**CH**$_3$)$_3$) and 24.2, 23.6 (2s, **CH**$_2$**CH**$_2$N); m/z 230, 191, 174, 130 and 70.

N-Boc-(S)-prolinol (S)-**11** - White crystalline solid (92%); $[\alpha]_D^{20}$ -49.9 (c = 1.1, $CHCl_3$), lit[8] $[\alpha]_D$ -48.83 (c = 1.2, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 4.77 (1H, dd, **CH**N), 3.95 (1H, br d, CH$_2$**OH**), 3.64-3.58 (2H, m, **CH**$_2$N), 3.46, 3.32 (2H, m, **CH**$_2$OH), 2.05-1.98 and 1.98-1.72 (4H, m, **CH**$_2$**CH**$_2$CH$_2$N) and 1.48 (9H, s, C(CH$_3$)$_3$); δ_C (62.9 MHz, $CDCl_3$) (two rotamers, population 88:12) 156.9 (s, **C**O$_2$C(CH$_3$)$_3$), 79.9 (s, **C**(CH$_3$)$_3$), 67.2, 64.5 (2s, **CH**$_2$OH), 60.0, 58.9 (2s, **CH**N), 47.3 (s, **CH**$_2$N), 28.5 (s, **CH**$_2$CHN), 28.3 (s, C(**CH**$_3$)$_3$) and 23.9 (s, **CH**$_2$**CH**$_2$N); δ_C (CD_3CN, 25°C, two rotamers, population 67:33).

N-Boc-(S)-prolinal (S)-**2** - Colourless oil (100%): δ_H (300 MHz, $CDCl_3$) (two rotamers, population 2:3) 9.54, 9.45 (1H, d, J 3 Hz and 2 Hz, **CH**O), 4.18, 4.04 (1H, m, **CH**N), 3.56, 3.47 (2H, m, **CH**$_2$N), 1.94, 1.89 (4H, m, NCH**CH**$_2$**CH**$_2$) and 1.46, 1.38 (9H, s, C(**CH**$_3$)$_3$).

Reaction of the diethylaluminium enolate of (RS)-**6** *with N-Boc-(S)-prolinal* (S)-**2** - The lithium enolate of (RS)-**6** was generated from 2.00 g (4.40 mmol) of the complex by addition of butyllithium (4.0 ml, 6.40 mmol). After stirring at -78°C for 0.5 h, diethylaluminium chloride (8.8 ml, 17.6 mmol) was added and the reaction warmed to -40°C for 2 h, causing a colour change from deep red to orange as transmetallation occurred. The solution was cooled to -100°C and aldehyde (S)-**2** (875mg, 4.40 mmol) was added dropwise as a solution in THF (2 ml). The reaction was stirred at -100°C for 2 h during which time the colour became yellow. The reaction was quenched with methanol (2 ml) and all solvents evaporated under reduced pressure. Chromatography on alumina (grade II) with light petroleum : ether (1:1) as eluant gave 935 mg of starting complex **6**. Subsequent elution with an ether-ether:ethyl acetate (1:1) gradient gave partial separation of diastereoisomers but this was incomplete. The total yield of all four diastereoisomers **12-15** was 1.215 g (79%, allowing for the recovered starting complex) in the ratio shown in Table 1.

Reaction of the tin (II) enolate of (RS)-**6** *with N-Boc-(S)-prolinal* (S)-**2** - The lithium enolate of RS-6 was generated from 1.00 g (2.20 mmol) of complex **6** as before. After stirring at -78°C for 0.5 h, a suspension of tin (II) chloride (580 mg, 3.10 mmol) in THF (2 ml) was introduced by cannula and the reaction warmed to -40°C for 2 h, after which the deep red colour of the lithium enolate had changed to the orange-brown characteristic of the stannous enolate. The reaction was cooled to -78°C and N-Boc-(S)-prolinal (S)-**2** (450 mg 2.26 mmol) added. The reaction was allowed to warm from -78°C to ambient temperature over a period of 15 h and then quenched by addition of methanol (2 ml). Work-up and chromatography as before gave 506 mg of starting complex **6** with 575mg (81% - based on recovered starting complex) of a mixture of diastereoisomers **12-15** in the ratio shown in Table 1. (Found C, 65.95; H, 6.50; N, 2.08. $C_{36}H_{40}FeNO_5P$ requires C, 66.16; H, 6.17; N, 2.14%).

(R,R,S)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2CH(OH)C_8H_{16}NO_2$] (R,R,S)-**13**, υ_{max} (CH_2Cl_2) 3400 (OH), 1918 (C=O), 1592 (C=O) and 1680 cm^{-1} ($NCO_2{}^tBu$); δ_H (300 MHz, d_6-DMSO, 360K) 7.50-7.30 (15H, m, PPh_3), 4.46 (5H, d, J 1.2 Hz, Cp), 4.00 (1H, m, NC**H**), 3.70 (1H, d, J 3.8 Hz, CH(**OH**)), 3.52 (1H, m, C**H**(OH)), 3.22 (2H, m, NCH_2), 2.83, 2.53 (2H, ABX system, J_{AB} 15.5 Hz, J_{AX} 9.0 Hz, J_{BX} 3.8 Hz, $COCH_2$), 1.72-1.62 (4H, m, $NCH_2CH_2CH_2$) and 1.42 (9H, s, $C(CH_3)_3$); δ_C (62.9 MHz, d_6-DMSO, 360K) 220.1 (d, J_{PC} 30.4 Hz, Fe-(**C**O)), 155.1 (s, $NCO_2{}^tBu$), 136.1 (d, J_{PC} 43.3 Hz, PPh_3C_{ipso}), 133.3 (d, J_{PC} 9.8 Hz, PPh_3C_{ortho}), 129.8 (s, PPh_3C_{para}), 128.1 (d, J_{PC} 9.7 Hz, PPh_3C_{meta}), 85.1 (s, Cp), 84.7 (s, **C**H(OH)), 79.3 (s, **C**$(CH_3)_3$), 68.9 (s, $COCH_2$), 60.7 (s, NCH), 47.1 (s, NCH_2), 29.6, 26.6 (s, NCH_2CH_2) and 28.5 (s, C(**C**$H_3)_3$); δ_P (101.3 MHz, d_6-DMSO, 360K) 72.21; m/z 653 (M^+) and 625 (M^+-CO).

(S,S,S)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2CH(OH)C_8H_{16}NO_2$] (S,S,S)-**15** - υ_{max} (CH_2Cl_2) 3400 (OH), 1918 (C=O), 1592 (C=O) and 1680 cm^{-1} ($NCO_2{}^tBu$); δ_H (300 MHz, d_6-DMSO, 360K) 7.50-7.30 (15H, m, PPh_3), 4.48 (5H, d, J 1.2 Hz, Cp), 4.00 (1H, m, NC**H**), 3.70 (1H, br s, CH(**OH**)), 3.61 (1H, m, C**H**(OH)), 3.12 (2H, m, NCH_2), 2.83, 2.53 (2H, m, $COCH_2$), 1.79 (4H, m, $NCH_2CH_2CH_2$) and 1.43 (9H, s, $C(CH_3)_3$); δ_C (62.9 MHz, d_6-DMSO, 360K) 220.1 (d, J_{PC} 30.4 Hz, Fe-(**C**O)), 155.0 (s, $NCO_2{}^tBu$), 136.1 (d, J_{PC} 43.3 Hz, PPh_3C_{ipso}), 133.3 (d, J_{PC} 9.8 Hz, PPh_3C_{ortho}), 129.8 (s, PPh_3C_{para}), 128.1 (d, J_{PC} 9.7 Hz, PPh_3C_{meta}), 85.3 (s, Cp), 84.7 (s, CH(OH)), 79.3 (s, C$(CH_3)_3$), 69.5 (s, $COCH_2$), 59.4 (s, NCH), 47.1 (s, NCH_2), 25.6, 24.1 (s, NCH_2CH_2) and 28.5 (s, C$(CH_3)_3$); δ_P (300 MHz, d_6-DMSO, 360K) 71.59; m/z 653 (M^+) and 625 (M^+-CO).

(S,R,S)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2CH(OH)C_8H_{16}NO_2$] (S,R,S)-**14** - (S,R,S)-**14** was prepared from homochiral (S)-**6** (300 mg, 0.66 mmol) by the procedure described above for the racemic diethylaluminium enolate of complex (RS)-**6**. Recovery of starting complex amounted to 53 mg whilst the yield of (S,R,S)-**12** was 281 mg (79%). The other diastereoisomer (S,S,S)-**15** could not be detected by ^{1}H n.m.r. spectroscopy, the >99:<1 ratio is shown in Table 1. (Found C, 66.29; H, 6.44; N, 1.98. $C_{36}H_{40}FeNO_5P$ requires C, 66.16; H, 6.17; N, 2.14%); υ_{max} (CH_2Cl_2) 3200 (OH), 1915 (C=O), 1580 (C=O) and 1680 cm^{-1} ($NCO_2{}^tBu$); δ_H (300 MHz, d_6-DMSO, 360K) 7.47-7.37 (15H, m, PPh_3), 4.45 (5H, d, J 1 Hz, Cp), 4.45 (1H, m, NC**H**), 3.99 (1H, br s, CH(O**H**)), 3.75 (1H, m, C**H**(OH)), 3.31 (2H, m, NCH_2), 3.13, 2.58 (2H, ABX system, J_{AB} 16.7 Hz, J_{AX} 9.0 Hz, J_{BX} 2.8 Hz, $COCH_2$), 1.80-1.30 (4H, m, $NCH_2CH_2CH_2$) and 1.41 (9H, s, $C(CH_3)_3$); δ_C (62.9 MHz, d_6-DMSO, 360K) 220.3 (d, J_{PC} 31.1 Hz, Fe-(CO)), 155.5 (s, $NCO_2{}^tBu$), 136.5 (d, J_{PC} 43.3 Hz, PPh_3C_{ipso}), 133.5 (d, J_{PC} 9.8 Hz, PPh_3C_{ortho}), 130.0 (s, PPh_3C_{para}), 128.3 (d, J_{PC} 9.3 Hz, PPh_3C_{meta}), 85.6 (s, Cp), 79.2 (s, $C(CH_3)_3$), 70.0 (s, CH(OH)), 69.1 (s, $COCH_2$), 60.8 (s, NCH), 47.0 (s, NCH_2), 27.0, 23.3 (s, $NCH_2CH_2CH_2$) and 28.7 (s, $C(CH_3)_3$); δ_P (101.3 MHz, d_6-DMSO, 360K) 72.28, 71.76; m/z 653 (M^+) and 625 (M^+-CO).

(R,S,S)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2CH(OH)C_8H_{16}NO_2$] (R,S,S)-**12** - (R,S,S)-**12** was prepared in an analogous fashion from the R enantiomer of complex **6**. Chromatography gave 67 mg of starting complex (R)-**6** and 251 mg of (R,S,S)-**12** as a 97:3 mixture with (R,R,S)-**13** (75%). (Found C, 66.18; H, 6.28; N, 2.18. $C_{36}H_{40}FeNO_5P$ requires C, 66.16; H, 6.17; N, 2.14%); υ_{max} (CH_2Cl_2) 3200 (OH), 1915 (C=O), 1605 (C=O) and 1680 cm^{-1} ($NCO_2{}^tBu$); δ_H (300 MHz, d_6-DMSO, 360K) 7.45-7.38 (15H, m, PPh_3), 4.46 (5H, d, J 1.2 Hz, Cp), 4.46 (1H, m, NC**H**), 3.96 (1H, br s, CH(O**H**)), 3.78 (1H, m, C**H**(OH)), 3.59, 3.36 (2H, m, NCH_2), 3.09, 2.56 (2H, ABX system, J_{AB} 16.2 Hz, J_{AX} 9.9 Hz, J_{BX} 1.6 Hz, $COCH_2$), 1.90-1.60 (4H, m, $NCH_2CH_2CH_2$) and 1.40 (9H, s, $C(CH_3)_3$); δ_C (62.9 MHz, d_6-DMSO, 360K) 220.3 (d, J_{PC} 31.1 Hz, Fe-(CO)), 155.0 (s, $NCO_2{}^tBu$), 136.4 (d, J_{PC} 42.9 Hz, PPh_3C_{ipso}), 133.3 (d, J_{PC} 9.7 Hz, PPh_3C_{ortho}), 129.7 (s, PPh_3C_{para}), 128.0 (d, J_{PC} 9.8 Hz, PPh_3C_{meta}), 85.5 (s, Cp), 79.5 (s, $C(CH_3)_3$), 71.2 (s, CH(OH)), 69.2 (s, $COCH_2$), 61.0 (s, NCH), 46.9 (s, NCH_2), 27.6, 23.8 (s, $NCH_2CH_2CH_2$) and 28.5 (s, $C(CH_3)_3$); δ_P (101.3 MHz, d_6-DMSO, 360K) 72.90, 72.21; m/z 653 (M^+) and 625 (M^+-CO).

(1R,8S)-1-Hydroxypyrrolizidin-3-one (R,S)-**5** -

A 2.0M aqueous solution of *p*-toluenesulphonic acid (5 ml) was stirred with 250 mg (0.38 mmol) of (S,R,S)-**12** overnight at ambient temperature causing some darkening of colour. The excess acid was neutralised by addition of a solution of sodium bicarbonate (3.5 g) in water (40 ml). The mixture was extracted with dichloromethane and the yellow organic phase filtered through celite and evaporated to dryness. Chromatography on alumina (grade V) with dichloromethane followed by dichloromethane : methanol (9:1) gave the (S,R,S)-**16** as an orange foam (199 mg, 93%). δ_H (300 MHz, $CDCl_3$) 7.52-7.34 (15H, m, PPh_3), 4.45 (5H, d, J 1.4 Hz, Cp). 3.29 (1H, m, NC**H**), 2.94-2.88 (3H, m, C**H**(OH) and NCH_2), 2.78-2.63 (2H, m, $COCH_2$), 1.70-1.50 (4H, m, $NCH_2CH_2CH_2$); m/z 554 (MH^+).

(S,R,S)-**16** (199 mg, 0.36 mmol) was dissolved in dry dichloromethane (10 ml) and cooled to -78°C. A solution of bromine (20 µl, 0.39 mmol) in dichloromethane (1 ml) was added dropwise. The resulting dark green

solution was stirred (-78°C, 0.5 h) before addition of triethylamine (70 μl, 0.5 mmol). After warming to ambient temperature and stirring for a further 1 h, the solution was evaporated to dryness. The residue was redissolved in a small volume of dry dichloromethane on chromatographed on alumina (grade V), elution with dichloromethane removing both triphenylphosphine and [(η^5-C_5H_5)Fe(CO)(PPh_3)Br]. Material remaining on the column was eluted with ethyl acetate:methanol (9:1). The crude crystalline residue was purified by flash chromatography on silica (eluting with ethyl acetate:light petroleum (1:1)) to give (R,S)-**5** (31 mg, 61% from (S,R,S)-**16**).
m.p. 81-82°C, lit[4] m.p. 84-86°C; $[\alpha]_D^{20}$ -97.0 (c = 0.3, $CHCl_3$), lit[4] $[\alpha]_D$ -91.5 (c = 1.0, $CHCl_3$); (Found C, 59.70; H, 7.94; N, 9.62. $C_7H_{11}NO_2$ requires C, 59.56; H, 7.85; N, 9.62%); υ_{max} (CH_2Cl_2) 3350 (OH) and 1690 cm^{-1} (C=O)); δ_H (500 MHz, $CDCl_3$) 4.22 (1H, m, **H**-1), 3.74 (1H, m, **H**-8), 3.54 (1H, m, **H**-5β), 3.22 (1H, d, J 5.1 Hz, **OH**), 3.03 (1H, m, **H**-5α), 2.73 (2H, d, J 8.3 Hz, **H**-2α, **H**-2β), 2.14 (1H, m, H-7α), 2.08-1.95 (2H, m, H-6α, 6β) and 1.45 (1H, m, H-7α) (assignments were supported by COSY data); δ_C 172.5 (s, **C**-3), 73.3 (s, **C**-1), 69.3 (s, **C**-8), 44.4 (s, **C**-2), 41.7 (s, **C**-5), 29.9 and 26.6 (2s, **C**-6, **C**-7); m/z 142 (MH^+), 112 and 70.

(1S,8S)-1-Hydroxypyrrolizidin-3-one (S,S)-7

In an analogous procedure the 97:3 mixture of (R,S,S)-**12** and (R,R,S)-**13** was decomplexed over two steps to give (S,S)-**7** and (R,S)-**5** (97:3). A single recrystallisation gave diastereoisomerically pure (S,S)-**7** (40%). m.p. 118-119°C; $[\alpha]_D^{20}$ -48.8 (c = 0.3, $CHCl_3$); (Found C, 59.18; H, 7.94; N, 9.64. $C_7H_{11}NO_2$ requires C, 59.56; H, 7.85; N, 9.62%); ν_{max} (CH_2Cl_2) 3300 (OH) and 1685 cm^{-1} (C=O); δ_H (500 MHz, $CDCl_3$) 4.41 (1H, m, **H**-1), 4.00 (1H, m, **H**-8), 3.56 (1H, m, H-5β), 3.86 (1H, d, J 6.2 Hz, **OH**), 3.06 (1H, m, H-5), 2.98 (1H, ddt, J 16.7, 4.9 and 1.3 Hz, H-2α), 2.44 (1H, d, J 16.7 Hz, H-2β), 2.17-2.05 (3H, m, H-6α, 6β, 7β) and 1.45 (1H, m, H-7α) (assignments were supported by COSY data); δ_C (62.9 MHz, $CDCl_3$) 173.3 (s, **C**-3), 68.2 (s, **C**-1), 67.0 (s, **C**-8), 45.7 (s, **C**-2), 41.5 (s, **C**-5), 27.2 and 23.0 (2s, **C**-6, **C**-7); m/z 142 (MH^+), 112 and 70.

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