Chiral Succinate Enolate Equivalents for the Asymmetric Synthesis of α-Alkyl Succinic Acid Derivatives

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Alkylation of the chiral iron succinoyl complex $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)COCH_2CH_2CO_2Bu^t]$ by sequential treatment with butyl-lithium and alkyl halides takes place highly regio- and stereoselectively to generate β-alkyl substituted iron succinoyl complexes. These differentially protected chiral succinoyl complexes undergo oxidative decomplexation to provide homochiral α-alkyl succinic acid derivatives in high yield.

The need to obtain chiral synthetic intermediates such as sustituted β-lactams,[1] β- and γ-lactones,[2] and cyclopentanoids,[3] in homochiral form, has prompted much research into the synthesis of chiral succinates and other 1,4-dicarbonyls. Alkyl succinic acid derivatives are also important chiral subunits of many pseudopeptides which have proved effective as inhibitors of various zinc-based metallo-enzymes.[4–6] As such, these compounds could be useful for the treatment of various conditions including arthritis or cancer given, for example, their recently observed *in vivo* antimetastatic activity.[5] The pseudopeptide Actinonin,[7] an α-pentyl succinoyl derivative whose synthesis we have recently achieved, also displayed antibiotic activity *in vitro* against gram-positive and gram-negative bacteria.[8] Interestingly, L-benzylsuccinic acid itself is a known inhibitor of thermolysin[9] and carboxypeptidase A.[10]

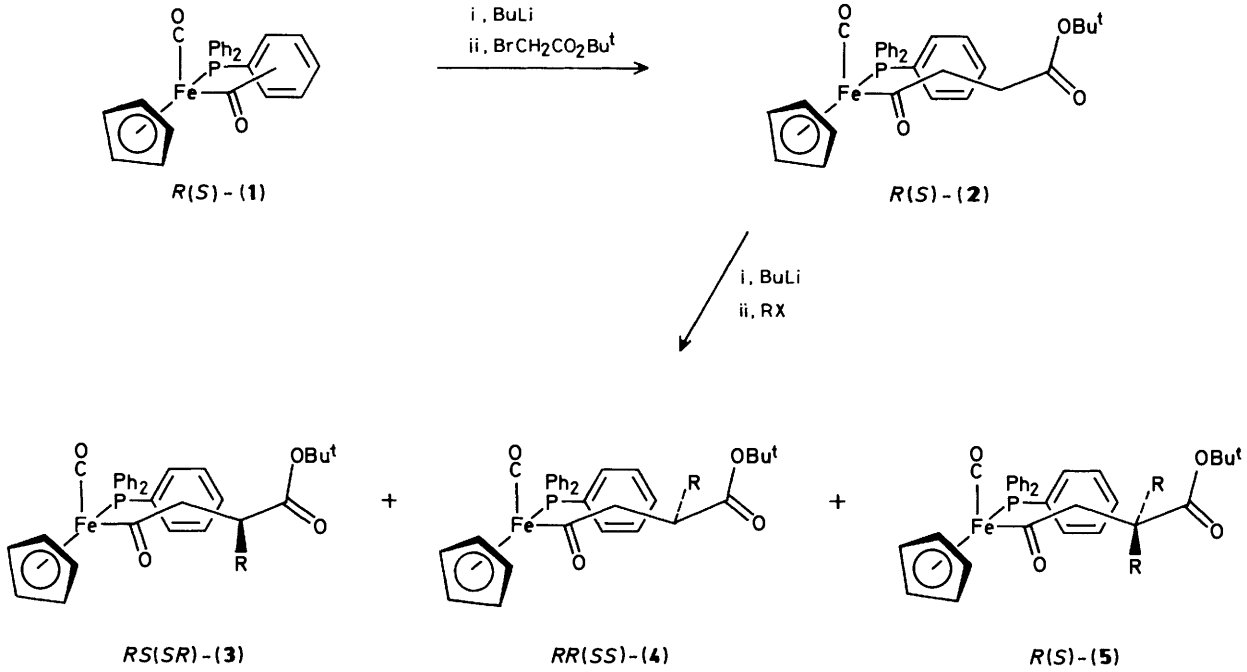
To date, most approaches towards the synthesis of chiral alkyl succinates require inefficient resolutions of diastereoisomeric mixtures,[11] while others involve the multi-step transformation of naturally occurring substrates[12] or the reduction of unsaturated carboxylates by hydrogenation under various conditions.[13] Only isolated cases have been reported where chiral appendages have been employed to aid in the generation of chiral alkyl-substituted succinate or α-hydroxysuccinate derivatives.[14,15] None of these, however, leads to differentially protected derivatives of proven stereochemical integrity.

Table 1.

RX	Main product	Crude ratio (**3**)/(**4**)	Pure (**3**) Yield (%)	Pure (**3**) D.e. (%)	Yield (**5**) (%)
MeI	(**3a**)	4:1	61	98	—
AllylI	(**3b**)	2:1	57	99	—
BuI	(**3c**)	15:1	77	97	8
Bu^iI	(**3d**)	15:1	79	100	<2
$C_5H_{11}I$	(**3e**)	22:1	82	100	<2
$PhCH_2Cl$	(**3f**)	10:1	83	97	—

We present here a simple highly efficient method for the regio- and diastereo-selective preparation of homochiral monoalkyl succinic acid derivatives based on the regio- and stereo-selective elaboration of the chiral iron acetyl complex $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)COCH_3]$ (**1**).

Deprotonation of the racemic iron acetyl complex *R*(*S*)-(**1**) with butyl-lithium in tetrahydrofuran (THF) at −78 °C followed by the rapid addition of t-butyl bromoacetate gave the iron succinoyl complex (**2**) in 96% yield. Treatment of complex *R*(*S*)-(**2**) with butyl-lithium in THF at −78 °C immediately gave a dark orange solution. Quenching with methyl iodide yielded a mixture of monomethylated iron succinoyl dia-



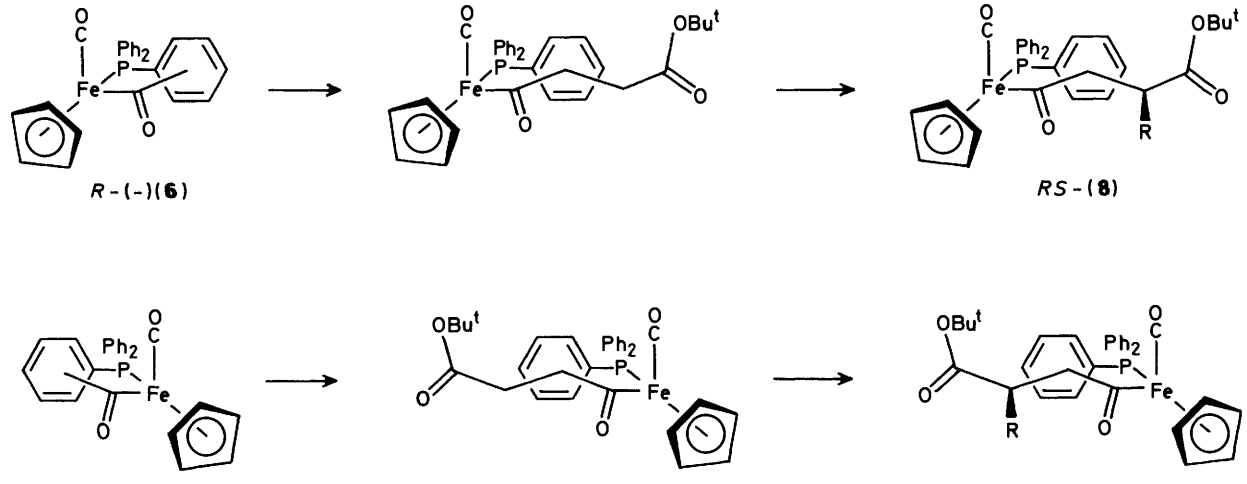
R(S)-(1) R(S)-(2) RS(SR)-(3) RR(SS)-(4) R(S)-(5)

stereoisomers (**3a**) and (**4a**) in the ratio 4:1. As expected, this reaction was totally regioselective, no evidence being obtained for alkylation α to the iron acyl function.[16] The products (**3a**) and (**4a**) were readily separated by medium pressure column chromatography on flash silica after elution with dichloromethane. The relative configuration of the major diastereoisomer (**3a**) was shown to be *RS*(*SR*), by single crystal *X*-ray structure analysis.[17]

Alkylation of the lithium enolate of succinoyl complex (**2**) was investigated with various other alkyl halides (Table 1). In most cases these reactions were found to be remarkably highly diastereoselective (Table 1). More importantly, simple column chromatography of the crude reaction mixture, using flash silica as the absorbent and dichloromethane as the eluant, furnished the main monoalkylated diastereoisomers (**3**) in high yield and in excellent diastereoisomeric excess (>97%). In some cases small quantities of readily separable dialkyl iron succinoyl complexes (**5**) were also formed. The stereochemistries of these products were assigned by correlation of their ^{1}H n.m.r. spectra with that of complex (**3a**).

Application of the previously described methodology to homochiral iron acyl complxes (**6**) and (**7**) has allowed us to prepare several homochiral iron succinoyl complexes (**8**) and (**9**) (Table 2).

The maintenance of stereochemical integrity during decomplexation was explored by reaction of homochiral iron succinoyl complexes (**8b**) and (**9b**) with *N*-bromosuccinimide (NBS) in the presence of (+)-α-methylbenzylamine. This resulted in the selective preparation of the homochiral succinate derivatives (**10**) {86%, $[\alpha]_D^{20}$ +42.9° (*c* 0.144 $CHCl_3$)} and (**11**) {90%, $[\alpha]_D^{20}$ +88.2° (*c* 0.173 $CHCl_3$)} both as single diastereoisomers as analysed by high field ^{1}H n.m.r. spectroscopy. Similarly decomplexation of complex (**9b**) with NBS in wet THF gave the homochiral succinic acid half ester (**12**) in 86% yield {$[\alpha]_D^{20}$ +16.7° (*c* 0.64 $CHCl_3$)}. Coupling of (**12**) with (+)-α-methylbenzylamine independently gave the amide (**11**). ^{1}H N.m.r. spectroscopic analysis of the amide showed it to be a single diastereoisomer and thus confirmed the homochirality of half ester (**12**). Treatment of (**12**) with trifluoroacetic acid provided (*R*)-2-(2-methylpropyl)succinic



R-(-)(6) RS-(8) S-(+)(7) SR-(9)

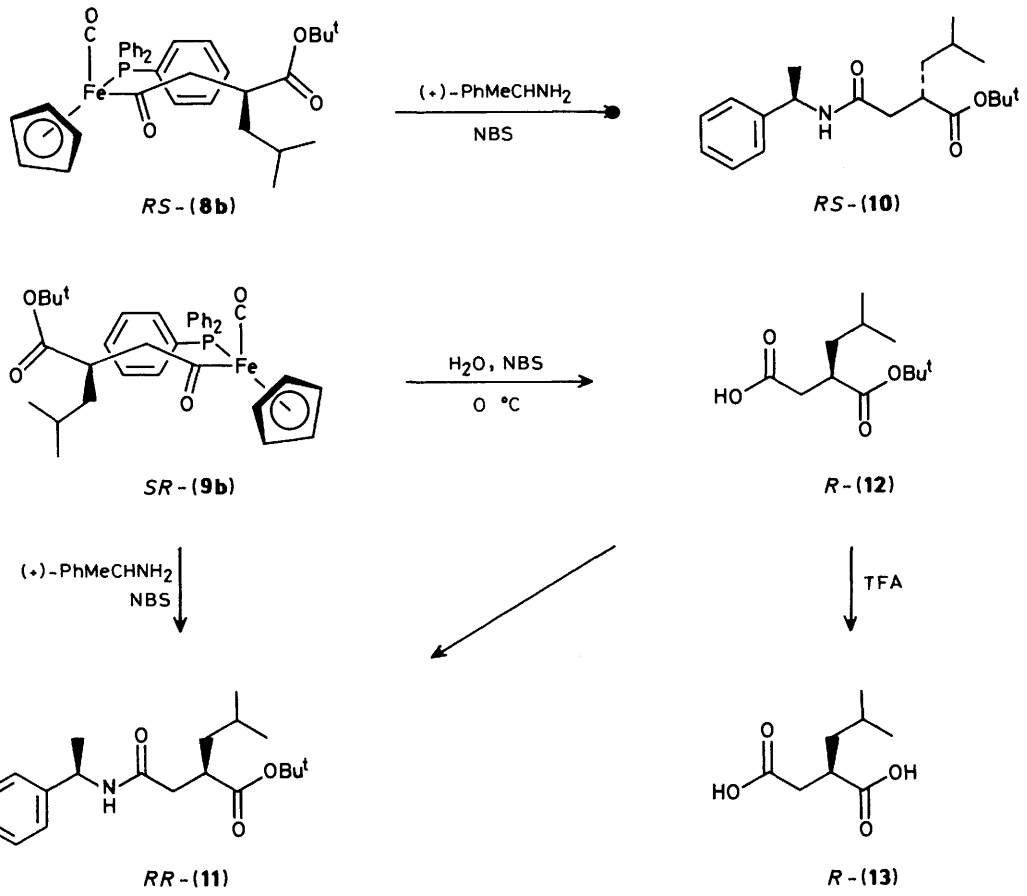


Table 2.

Product	R	Configuration	$[\alpha]_D^{20}(C_6H_6)$
(8a)	Me	*RS*	−49.4° (*c* 0.235)
(8b)	Bu^i	*RS*	−27.7° (*c* 0.235)
(9b)	Bu^i	*SR*	+24.7° (*c* 0.231)
(8c)	C_5H_{11}	*RS*	−28.5° (*c* 0.08)
(9c)	C_5H_{11}	*SR*	+28.7° (*c* 0.083)

acid (**13**) in practically quantitative yield {$[\alpha]_D^{20}$ +26.2° (*c* 1.01 EtOH); lit.,[18] $[\alpha]_D$ +26.8° (*c* 5.0 EtOH)}. By direct analogy, this result equally establishes the absolute stereochemistry of the succinates (**8b**), (**9b**), (**10b**), and (**11b**).*

Acknowledgements

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* (*R*)-2-(2-Methylpropyl)succinic acid, whose stereochemistry has previously been determined by the quasi-racemate method was shown to have a positive optical rotation: A. Fredga, *Tetrahedron*, 1960, **8**, 126.

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