Tetrahedron Letters 49 (2008) 7398–7402

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Investigations into the parallel kinetic resolution of acetyl mandelic acid

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ARTICLE INFO

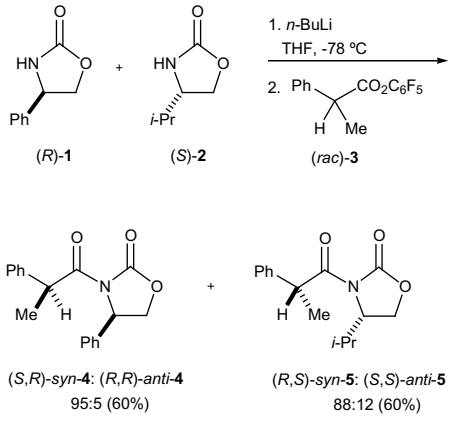
Article history:
Received 4 September 2008
Revised 3 October 2008
Accepted 14 October 2008
Available online 18 October 2008

ABSTRACT

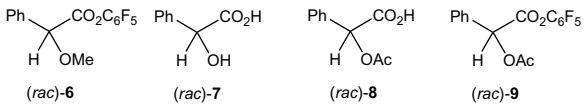
The resolution of a series of active esters (derived from acetyl mandelic acid) using an equimolar combination of *quasi*-enantiomeric oxazolidin-2-ones is discussed. The levels of diastereoselectivity and the facial selectivity were found to be dependent on the structural nature of the *pro*-leaving group.

The resolution and synthesis of pharmaceutically important[1] enantiomerically pure 2-phenylpropionic acid and its derivatives are well documented.[2–4] Over the last few years, we have been interested in the parallel kinetic resolution[5–7] of pentafluorophenyl 2-phenylpropionate (*rac*)-**3** (and its structurally related derivatives)[8] using an equimolar combination of *quasi*-enantiomeric[9] oxazolidin-2-ones (*R*)-**1** and (*S*)-**2** as resolving agents. Addition of pentafluorophenyl 2-phenylpropionate (*rac*)-**3** to a stirred solution of lithiated Evans oxazolidin-2-ones (formed by treating an equimolar combination of (*R*)-**1** and (*S*)-**2** with *n*-BuLi in THF at −78 °C) gave after 2 h, a separable diastereoisomeric mixture of oxazolidin-2-one adducts (*S*,*R*)-*syn*-**4** (in 60% yield with 90% de) and (*R*,*S*)-*syn*-**5** (in 60% yield with 78% de) (Scheme 1).

We recently extended[10] this methodology towards the parallel kinetic resolution of pentafluorophenyl 2-methoxy-2-phenyl-acetate (*rac*)-**6** (Scheme 2) using this combination of oxazolidin-2-ones (*R*)-**1** and (*S*)-**2** with some success leading to the corresponding oxazolidin-2-one adducts with up to 78% de. In an attempt to better understand these parallel kinetic resolutions, we were interested in the resolution of 2-hydroxycarboxylic acids, such as mandelic acid (2-hydroxy-2-phenyl-acetic acid) (*rac*)-**7** (Scheme 2). We chose to protect the *C*(2) hydroxyl substituent of mandelic acid (*rac*)-**7** as an acetate [acetyl mandelic acid (*rac*)-**8**] to limit its nucleophilic and acidic character (Scheme 2).[11]

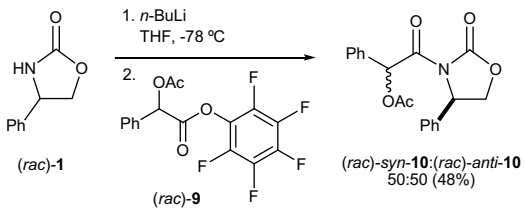


Scheme 1. Parallel kinetic resolution of active ester (*rac*)-**3** using *quasi*-enantiomeric oxazolidin-2-ones (*R*)-**1** and (*S*)-**2**.



Scheme 2. Active esters (*rac*)-**6** and (*rac*)-**9**.

We now report an extension to this methodology for the resolution of pentafluorophenyl 2-acetoxy-2-phenyl acetate (*rac*)-**9** using a *quasi*-enantiomeric combination of Evans' oxazolidin-2-ones (Scheme 2). We first investigated the level of mutual recognition between pentafluorophenyl 2-acetoxy-2-phenyl acetate (*rac*)-**9** [formed in 86% yield by addition of pentafluorophenol to a solution of DCC and 2-acetoxy 2-phenylacetic acid (*rac*)-**8**] and the (lithiated) oxazolidin-2-one (*rac*)-**1** (Scheme 3). Treatment of (*rac*)-**1** with *n*-BuLi in THF at −78 °C, followed by the addition of



Scheme 3. Mutual kinetic resolution of active ester (*rac*)-**9** using oxazolidin-2-one (*rac*)-**1**.

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0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.10.062

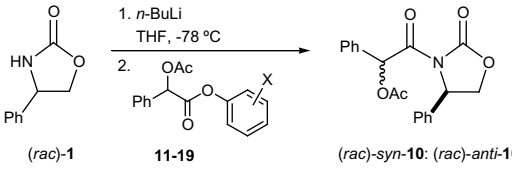
active ester (*rac*)-**9**, gave after 2 h, the corresponding oxazolidin-2-one adducts (*rac*)-*anti*- and (*rac*)-*syn*-**10** in 48% yield with no levels of mutual selection (Scheme 3). Intrigued by this apparent loss of stereoselection (78% de[10]→0% de) by the subtle substituent change from MeO- [in (*rac*)-**6**] to a AcO- [in (*rac*)-**9**], we next chose to investigate the structural nature of the *pro*-leaving group in an attempt to improve the levels of diastereoselection.

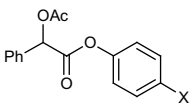
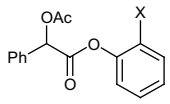
We first chose to screen the simplest active ester, phenyl 2-acetoxy-2-phenylacetate (*rac*)-**11**, with the (lithiated) oxazolidin-2-one (*rac*)-**1** under our standard mutual kinetic resolution conditions in order to get a measure of the natural diastereoselection (Scheme 4, entry 1). Deprotonation of the oxazolidin-2-one (*rac*)-**1** with *n*-BuLi in THF at −78 °C, followed by the addition of active ester (*rac*)-**11**, gave after 2 h, the corresponding oxazolidin-2-one adducts (*rac*)-*syn*- and (*rac*)-*anti*-**10** in 24% yield with good levels of mutual selection (ratio 87:13) (Scheme 4, entry 1). The *syn*-diastereoisomer (*rac*)-*syn*-**10** was found to be the major product. In an attempt to improve the overall yield of this resolution, we next screened a series of 4-halo-substituted active esters (*rac*)-**12**–**14** (X = F, Cl and Br), which contained an electron-withdrawing group to increase their electrophilicity and to aid their *pro*-leaving ability (Scheme 4, entries 2–4). Treatment of the oxazolidin-2-one (*rac*)-**1** with *n*-BuLi in THF at −78 °C, followed by the addition of active esters (*rac*)-**12–14**, gave after 2 h, the corresponding oxazolidin-2-one adducts (*rac*)-*syn*-**10** in higher yield (∼40%) with comparable levels of diastereoselection (76% de) (Scheme 4, entries 2–4). Whereas for a less electrophilic active ester, which contained an electron-donating 4-methoxyphenyl-substituent, such as (*rac*)-**15**, the reaction did not proceed under our standard reaction conditions (THF, −78 °C, 2 h) (Scheme 4, entry 5).

Our attention next turned to studying the mutual kinetic resolution of a related series of 2-substituted-phenyl active esters (*rac*)-**16**–**19** (X = F, Cl, Br and OMe) using the oxazolidin-2-one (*rac*)-**1** in an effort to better understand the steric and potential co-ordination effects (Scheme 4, entries 6–9). Addition of these active esters (*rac*)-**16**–**19** to a stirred solution of (lithiated) oxazolidin-2-one (*rac*)-**1** in THF at −78 °C, gave after 2 h, the corresponding oxazolidin-2-one adducts (*rac*)-*syn*- and (*rac*)-*anti*-**10** in 0–58% yields with little or no diastereoselection (0–14% de) (Scheme 4, entries 6–9). From this study, it was evident that a 2-substituted-phenolate *pro*-leaving group substantially lowered the levels of mutual recognition between the associated active ester and the parent oxazolidin-2-one (*rac*)-**1**. From this limited study, it appears that 4-chlorophenyl 2-acetoxy-2-phenylacetate (*rac*)-**13** was the optimum active ester for high levels of mutual recognition (Scheme 4, entry 3).

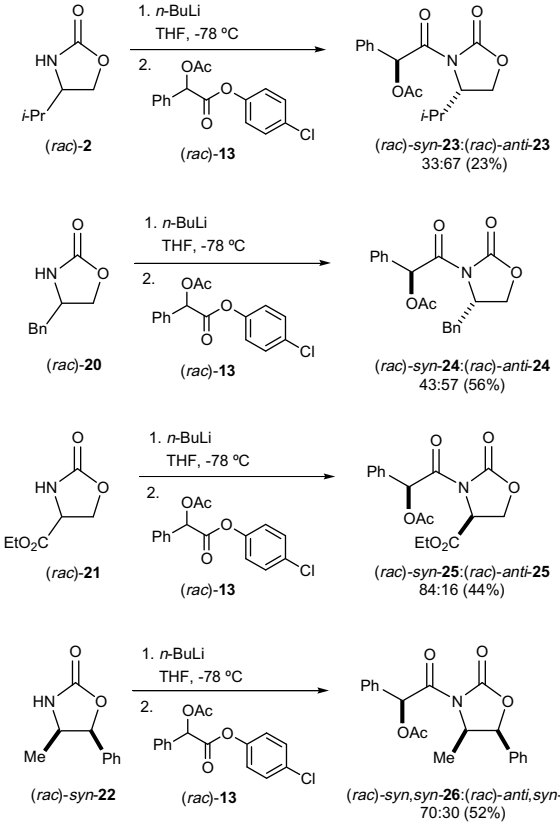
With this information in hand, we next focussed our attention on finding a complementary *quasi*-enantiomeric oxazolidin-2-one partner for **1** to enable efficient parallel kinetic resolution of 4-chlorophenyl 2-acetoxy-2-phenylacetate (*rac*)-**13** (Scheme 5). We chose to screen four structurally related oxazolidin-2-ones (*rac*)-**2**, (*rac*)-**20**–**21** and (*rac*)-*syn*-**22** under our standard mutual kinetic resolution conditions. Deprotonation of oxazolidin-2-ones (*rac*)-**2**, (*rac*)-**20**–**21** and (*rac*)-*syn*-**22** in THF at −78 °C with *n*-BuLi, followed by the addition of active ester (*rac*)-**13**, gave after 2 h, separable diastereoisomeric mixtures of oxazolidin-2-ones (*rac*)-*syn*- and (*rac*)-*anti*-**23** (in 23% yield with a ratio of 33:67), (*rac*)-*syn*- and (*rac*)-*anti*-**24** (in 56% yield with a ratio of 43:57), (*rac*)-*syn*- and (*rac*)-*anti*-**25** (in 44% yield with a ratio of 84:16) and (*rac*)-*syn*,*syn*- and (*rac*)-*anti*,*syn*-**26** (in 52% yield with a ratio of 70:30), respectively (Scheme 5).

These molecular recognition processes were found to be dependent on the structural nature and size of the *C*(4)-substituent within the oxazolidin-2-ones (*rac*)-**2**, (*rac*)-**20**–**21** and (*rac*)-*syn*-**22**. The diastereoselectivity changed from favouring *syn*- to *anti*-adduct formation for oxazolidin-2-ones, which contained a sterically demanding *C*(4)-sp^3-hybridised substituent; from 40% de favouring *syn*-**26** [for (*rac*)-*syn*-**22**], 14% de favouring *anti*-**24** [CH_2Ph in (*rac*)-**20**], through to 34% de favouring *anti*-**23** [$CHMe_2$ in (*rac*)-**2**] (Scheme 5). By comparison, oxazolidin-2-ones, such as (*rac*)-**1** and (*rac*)-**21**, which contained a *C*(4)-sp^2-hybridised substituent fa-



Entry	Active esters		*syn*-**10**:*anti*-**10**	Yield
1		(*rac*)-**11**; X = H	87:13	24%
2		(*rac*)-**12**; X = F	87:13	45%
3		(*rac*)-**13**; X = Cl	88:12	40%
4		(*rac*)-**14**; X = Br	87:13	42%
5		(*rac*)-**15**; X = OMe	—	0%
6		(*rac*)-**16**; X = F	57:43	40%
7		(*rac*)-**17**; X = Cl	50:50	58%
8		(*rac*)-**18**; X = Br	47:53	36%
9		(*rac*)-**19**; X = OMe	—	0%

Scheme 4. Mutual kinetic resolution of active esters (*rac*)-**11–19** using oxazolidin-2-one (*rac*)-**1**.



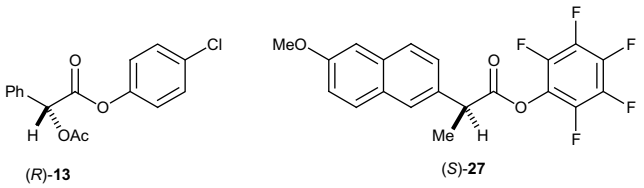
Scheme 5. Mutual kinetic resolution of active ester (*rac*)-**13** using oxazolidin-2-ones (*rac*)-**2**, (*rac*)-**20–21** and (*rac*)-*syn*-**21**.

voured *syn*-adducts **10** and **25** with 74% de and 68% de, respectively (Schemes 4 and 5).

With the completion of this preliminary study, we now turned our attention towards the parallel kinetic resolution of pentafluorophenyl 2-acetoxy-2-phenyl acetate (*rac*)-**13** using a combination of *quasi*-enantiomeric oxazolidin-2-ones. For our study, we chose to investigate the use of two combinations of oxazolidin-2-ones, namely a mismatched combination [(*R*)-**1** and (*S*)-**2**] and a matched combination [(*S*)-**1** and (*S*)-**21**], to better understand their relative dominance (Schemes 6 and 7).

For the mismatched combination of oxazolidin-2-ones (*R*)-**1** and (*S*)-**2**, treatment with *n*-BuLi in THF at −78 °C, followed by the addition of active ester (*rac*)-**13**, gave a separable combination of oxazolidin-2-ones (*S*,*R*)-*syn*- and (*R*,*R*)-*anti*-**10** [in 48% yield in a 83:17 ratio derived from (*R*)-**1**] and (*R*,*S*)-*syn*- and (*S*,*S*)-*anti*-**23** [in 45% yield in a 53:47 ratio derived from (*S*)-**2**] (Scheme 6). The oxazolidin-2-one (*R*)-**1** was found to be stereochemically more dominant than its *quasi*-enantiomeric partner (*S*)-**2** leading to the corresponding oxazolidin-2-ones (*S*,*R*)-*syn*-**10** [with moderate levels of diastereocontrol (66% de)] and (*R*,*S*)-*syn*-**23** [with poor levels of diastereocontrol (6% de)] (Scheme 6). Whereas for the matched combination of oxazolidin-2-ones (*S*)-**1** and (*S*)-**21**, these resolved efficiently the active ester (*rac*)-**13**, to give the corresponding oxazolidin-2-one adducts (*R*,*S*)-*syn*-**10** (in 64% yield with 70% *d.e.*) and (*S*,*S*)-*syn*-**25** (in 59% yield with 70% de) (Scheme 7). Evidently, each component of this combination of oxazolidin-2-ones resolved each enantiomer of the active ester (*rac*)-**13** in a near equal and opposite fashion.

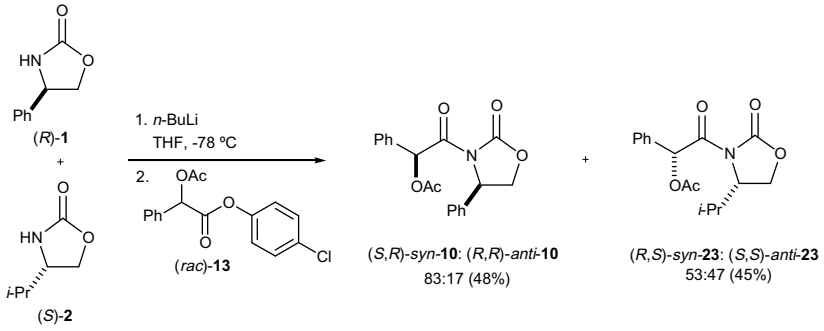
With this information in hand, we next turned our attention to probing the complementary parallel kinetic resolution of oxazolidin-2-ones (*rac*)-**1** and (*rac*)-**21** using a combination of *quasi*-enantiomeric active esters (*R*)-**13** and (*S*)-**27** (Schemes 8 and 9). Deprotonation of oxazolidin-2-ones (*rac*)-**1** and (*rac*)-**21** with *n*-BuLi in THF at −78 °C, followed by the addition of an equimolar combination of active esters (*R*)-**13** and (*S*)-**27**, gave after 2 h, the corresponding oxazolidin-2-one adducts (*R*,*S*)-*syn*-**10** (in 58% yield with 86% de) and (*S*,*R*)-*syn*-**28** (in 66% yield with 82% de) [for (*rac*)-**1**], and (*R*,*R*)-*syn*-**25** (in 53% yield with >90% de) and (*R*,*S*)-*syn*-**29** (in 56% yield with 74% de) [for (*rac*)-**21**] (Scheme 9).[12] The levels of stereocontrol were found to be excellent and in line with those obtained for their corresponding mutual kinetic resolutions. These adducts were separated efficiently by column chromatography leading to the required diastereoisomerically pure *syn*-adducts in good yield {ΔR_F [light petroleum ether (bp 40–60 °C)/diethyl ether] ~0.1 [for (*rac*)-**1**] and 0.18 [for (*rac*)-**21**]}.



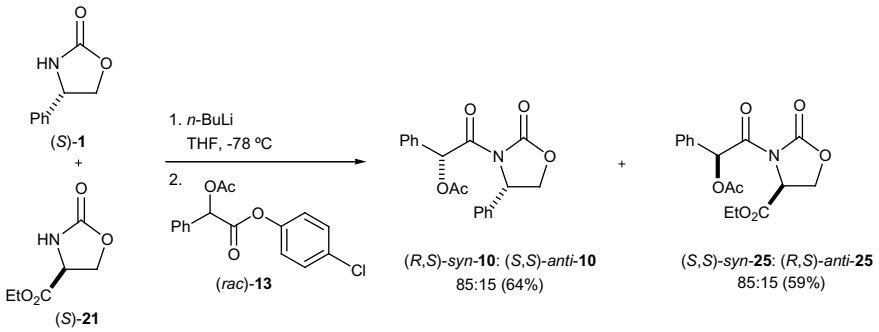
Scheme 8. *Quasi*-enantiomeric active esters (*R*)-**13** and (*S*)-**27**.

These types of resolutions can be performed using a combination of *quasi*-enantiomeric isotopomeric substrates, such as oxazolidin-2-ones (*R*)-**1** and (*S*)-[D_2]-**1**, and active esters (*R*)-**13** and (*S*)-[D_3]-**13** (Schemes 10 and 11). For example, deprotonation of an equimolar combination of oxazolidin-2-ones (*R*)-**1** and (*S*)-[D_2]-**1** using *n*-BuLi in THF at −78 °C, followed by the addition of active ester (*rac*)-**13**, gave a separable mixture of diastereoisomeric oxazolidin-2-ones (*S*,*R*)-*syn*-**10**/(*R*,*S*)-*syn*-[D_2]-**10** (with an isotopomeric ratio of 52:48 ± 2%) and (*R*,*R*)-*anti*-**10**/(*S*,*S*)-*anti*-[D_2]-**10** (with an isotopomeric ratio of 53:47 ± 2%) in 32% and 8% combined yields, respectively [(*S*,*R*)-*syn*-**10**/(*R*,*S*)-*syn*-[D_2]-**10**: (*R*,*R*)-*anti*-**10**/(*S*,*S*)-*anti*-[D_2]-**10** = 88:12] (Scheme 10).

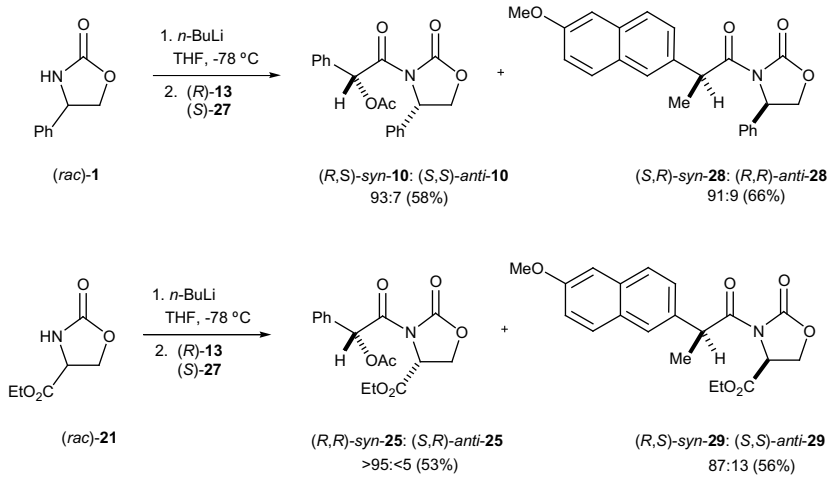
The complementary resolution of oxazolidin-2-one (*rac*)-**1** using a *quasi*-enantiomeric combination of isotopomers, (*R*)-**13** and (*S*)-[D_3]-**13**, gave similarly a separable mixture of diastereoiso-



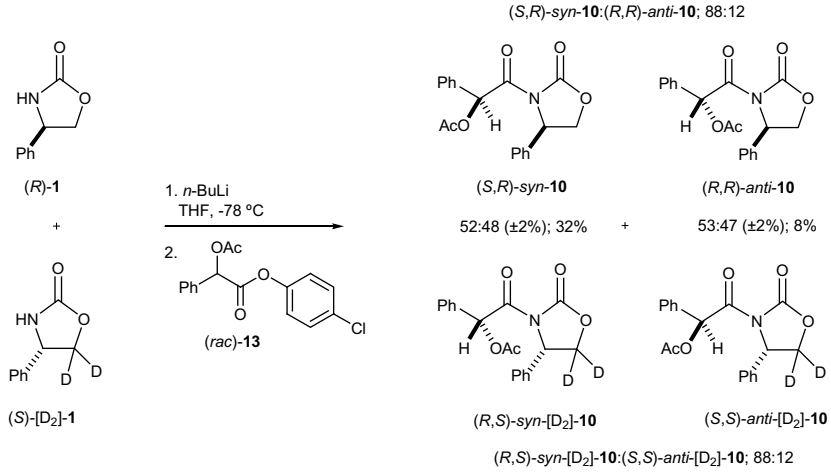
Scheme 6. Parallel kinetic resolution of active ester (*rac*)-**13** using a *mismatched* combination of oxazolidin-2-ones (*R*)-**1** and (*S*)-**2**.



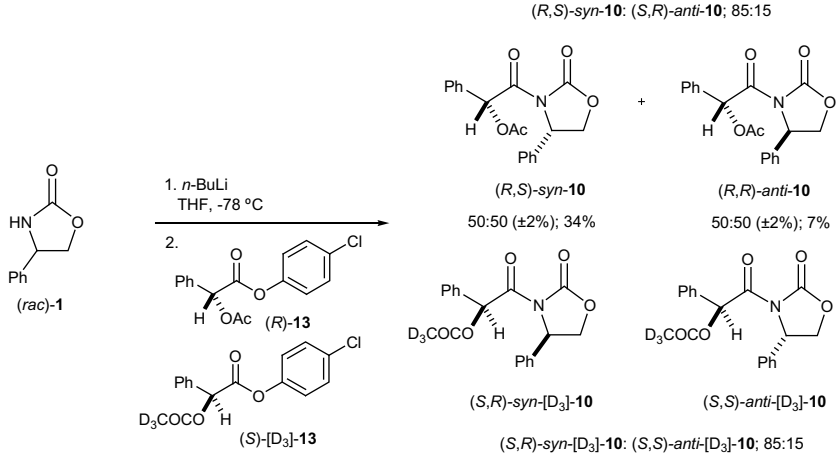
Scheme 7. Parallel kinetic resolution of active ester (*rac*)-**13** using a *matched* combination of oxazolidin-2-ones (*S*)-**1** and (*S*)-**21**.



Scheme 9. Parallel kinetic resolution of oxazolidin-2-ones (*rac*)-**1** and (*rac*)-**21** using *quasi*-enantiomeric active esters (*R*)-**13** and (*S*)-**27**.

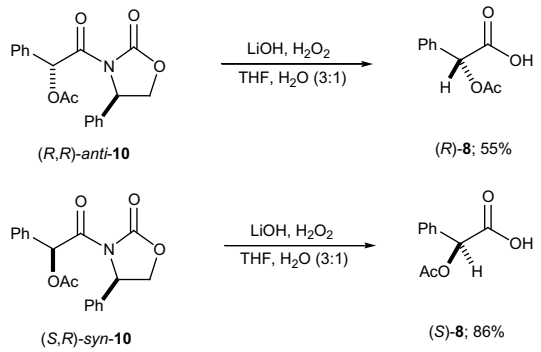


Scheme 10. Parallel kinetic resolution of active ester (*rac*)-**13** using a *quasi*-enantiomeric mixture of isotopomeric oxazolidin-2-ones (*R*)-**1** and (*S*)-[D_2]-**1**.



Scheme 11. Parallel kinetic resolution of oxazolidin-2-one (*rac*)-**1** using a *quasi*-enantiomeric mixture of isotopomeric active esters (*R*)-**13** and (*S*)-[D_3]-**13**.

meric oxazolidin-2-ones (*R*,*S*)-*syn*-**10**/(*S*,*R*)-*syn*-[D_3]-**10** (with an isotopomeric ratio of 50:50 ± 2%) and (*R*,*R*)-*anti*-**10**/(*S*,*S*)-*anti*-[D_3]-**10** (with an isotopomeric ratio of 50:50 ± 2%) in 34% and 7% combined yields, respectively [(*R*,*S*)-*syn*-**10**/(*S*,*R*)-*syn*-[D_3]-**10**: (*R*,*R*)-*anti*-**10**/(*S*,*S*)-*anti*-[D_3]-**10** = 85:15] (Scheme 11). These particular parallel kinetic resolutions behave similarly to their non-labelled mutual kinetic resolution involving the non-labelled parent oxazolidin-2-one (*rac*)-**1** and active ester (*rac*)-**13** (as shown in Scheme 4, entry 3). Interestingly, the use of *quasi*-enantiomeric isotopomers, such as (*R*)-**13**/(*S*)-[D_3]-**13**, as distinguishable enantiomers[13]



Scheme 12. Hydrolysis of oxazolidin-2-ones (*R*,*R*)-*anti*-**10** and (*S*,*R*)-*syn*-**10**.

allows the stereocontrol to be monitored efficiently by either ^{1}H NMR spectroscopy[14] or mass spectrometry.[15]

Access to both enantiomers of acetyl mandelic acid (*R*)- and (*S*)-**8** was achieved in good yields through simple hydrolysis [LiOH/H_2O_2 (1 equiv) in THF/H_2O (3:1)] of the corresponding oxazolidin-2-one adducts (*R*,*R*)-*anti*- and (*S*,*R*)-*syn*-**10**, respectively (Scheme 12). The absolute stereochemistry was assigned by comparison with the literature optical rotation values.[16] The optical purity was determined using a chiral shift NMR reagent, tris[3-(trifluoromethylhydroxy-methylene)-*d*-camphorato] europium(III).[17]

The nearest analogy to this work is that reported by Davies and co-workers.[18] They reported the kinetic resolution of 2-acetoxy-2-phenylacetyl chloride using 4-substituted and 4,5,5-trisubstituted oxazolidin-2-ones, such as (*S*)-**2**, to give predictably, the complementary oxazolidin-2-one adducts, such as *anti*-**23**, with moderate to excellent levels of diastereocontrol (~30–66% de). We have reported for 4-phenyloxazolidin-2-one (*rac*)-**1** a subtle change in the enantiomeric recognition process for active esters, such as (*rac*)-**13**, favouring formation of the *syn*-adduct **10** (in 76% de), whereas the related acid chloride[19] favoured formation of the *anti*-adduct **10** (in 66% de).

High levels of mutual recognition and diastereocontrol were achieved with (lithiated) oxazolidin-2-one **1** by removing the potential for competitive co-ordination and steric congestion at both the *C*(2) and *C*(6)-positions of the phenolate *pro*-leaving groups within the 2-acetyl mandelates (*rac*)-**12**–**14**. Active esters, such as (*rac*)-**9** and (*rac*)-**16**, which contain a halo-substituent at either the *C*(2) or the *C*(6)-positions, gave little or no levels of diastereocontrol. For good chemical yield, the *pro*-leaving group must have a moderately electron-withdrawing nature.

We had previously shown that high levels of *syn*-diastereoselection can be obtained using a related active ester, pentafluorophenyl 2-methoxy-2-phenyl-acetate (*rac*)-**6**. Replacing the 2-MeO substituent[10] [in (*rac*)-**6**] for a less co-ordinating 2-AcO substituent [in (*rac*)-**9**] lowered the overall level of diastereocontrol. Removing competitive co-ordination and steric congestion within the *pro*-leaving group[19,20] [as in (*rac*)-**12**] and thus promoting the co-ordinating nature of the 2-AcO substituent gave high levels of *syn*-diastereoselectivity (74% de).

In conclusion, we have reported the parallel kinetic resolution of racemic 2-acetoxy-2-phenyl acetic acid using an equimolar combination of *quasi*-enantiomeric oxazolidin-2-ones. For efficient resolution, this methodology was found to be dependent on the structural nature of the active ester and its *pro*-leaving group. High levels of mutual recognition were achieved using the 4-chlorophenyl active ester (*rac*)-**13** and an equimolar combination of *quasi*-enantiomeric oxazolidin-2-ones [e.g., (*S*)-**1** and (*S*)-**21**] leading to separable diastereoisomerically pure oxazolidin-2-one adducts **10** and **25** in good yields. The levels of diastereoselectivity and the facial selectivity were also found to be dependent on the structural nature of the oxazolidin-2-one.

Acknowledgements

We are grateful to Syngenta for funding (to S.C.), to the EPSRC for a studentship (to E.C.) and to the EPSRC National Mass Spectrometry Service (Swansea) for accurate mass determinations.

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