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Asymmetric synthesis of *trans*-4,5-dioxygenated cyclopentenone derivatives by organocatalyzed rearrangement of pyranones and enzymatic dynamic kinetic resolution

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ABSTRACT

Dioxygenated cyclopentenones are versatile building blocks for the synthesis of several natural products. Herein we report a direct asymmetric synthesis of *trans*-4,5-dioxygenated cyclopentenone derivatives through base-catalyzed rearrangement of pyranones followed by dynamic kinetic resolution. Milder conditions than previously reported for this rearrangement have been found regarding amine base catalysis, solvent and temperature effects. All data supports a mechanism involving cyclization of an intermediate formed by electrocyclic ring opening of a pyranone-derived enol. We have developed conditions for asymmetric synthesis of *trans*-4-*tert*-butoxy-5-hydroxycyclopent-2-enone, in 81% yield and 95% ee, and analogous dioxygenated cyclopentenones, via a lipase induced dynamic kinetic resolution.

1. Introduction

4,5-Bifunctionalized cyclopent-2-enones are versatile building blocks for natural products owing to their highly functionalized five-membered ring structure. In addition to their existing functional groups at C-4 and C-5, they can be further manipulated by 1,2 nucleophilic addition to the ketone at C-1, metal-catalysed coupling at C-2 and 1,4 conjugate addition to C-3. The *cis* dioxygenated cyclopentenones isomers have been used as intermediates in syntheses of several antiviral nucleosides, such as pentenomycin I, neplanocin A, aristeromycin and their analogues.[1–11] The *trans*-dioxygenated cyclopentenones are valuable for syntheses of antitumour antibiotics, such as the neocarzinostatin chromophore, kedarcidin chromophore and maduropeptin chromophore[12–18] as well as other antibiotics, such as trehazolin,[19] terrein[20] and (−)-epipentenomycin I.[21,22]

The versatility of oxygenated cyclopentenone scaffolds for synthesis is well recognised.[23] Recently, some methods for obtaining monohydroxylated cyclopentenones were reported for prostanoid syntheses[24–28] including a direct rearrangement from substituted furfuryl alcohols.[29–31] Lipase-catalyzed acylation is a well established procedure for the Dynamic Kinetic Resolution (DKR) of monohydroxylated cyclopentenones,[22,26,30,32–40] and indeed most approaches towards enantiopure dioxygenated cyclopentenones have evolved from that knowledge. These chemoenzymatic methods include those described by Johnson et al.,[41] Toyama et al.[42] and Klomklao et al.[22] By contrast, with the exception of some interesting photochemical rearrangements of 3-hydroxy-4-pyranones[20] and an application of Pauson–Khand followed by dihydroxylation,[43] most purely chemical methods tend to rely on available chiral starting materials and/or achieve their enantiomerically enriched target molecules through lengthy synthetic routes.[23,44–46]

Our work on the synthesis of Neocarzinostatin chromophore A required the synthesis of enantiomerically pure *trans*-dioxygenated cyclopentenone (−)-**3**.[16] To address that we became interested on a pyranone rearrangement reported by Mucha and Hoffmann.[47] Our previous studies on this pyranone rearrangement established a process to obtain cyclopentenone (±)-**3** in 78% yield from pyranone **2**, in turn available from furfuryl alcohol **1** (Scheme 1). This method can, however, lead to the undesirable formation of the

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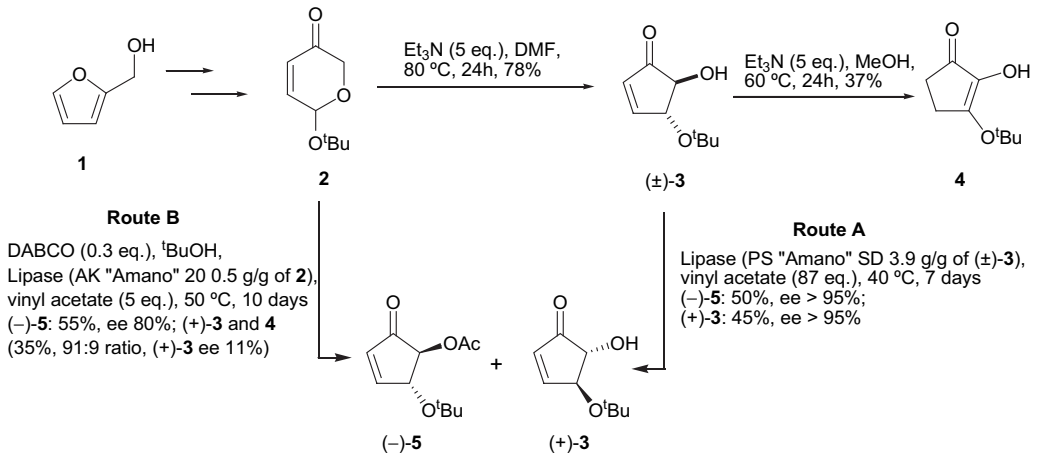


Scheme 1. Synthesis of enantiomerically pure *trans*-dioxygenated cyclopentenone (−)-**5** via either a two-step synthesis (route A) or direct transformation from pyranone **2** (route B).[16,50]

isomer **4** if methanol is used as solvent.[16,48] The synthetic utility of (±)-**3** has been demonstrated by nucleophilic and conjugate additions, intermolecular cycloaddition, free radical cyclization and palladium mediated coupling reactions.[49] In order to extend this work into the asymmetric synthesis arena, we established the synthesis of enantiomerically pure (−)-**3** in 50% yield and >95% ee via a classic lipase-catalyzed kinetic resolution.[50]

Recently, we have reported further developments of this kinetic resolution in which pyranone rearrangement and concomitant lipase-catalyzed acylation can be used to afford acetylated cyclopentenone (−)-**5** with 55% yield and 80% ee alongside observed racemization of (+)-**3** (Scheme 1, route B).[51] We have also reported a remarkable solvent effect that has allowed us to effect the pyranone rearrangement by amine organocatalysis, and this suggested to us that it might be possible to carry out a concomitant DKR in a one-pot version of this asymmetric transformation to achieve complete conversion of the racemic starting material into the target enantiomer.[51]

Herein we now report our full study on the asymmetric synthesis of functionalised cyclopentenones in which we have assessed the effect of amine base, solvent and temperature and carried out a study on the enzymatic resolution step. Together these have enabled us to establish a new methodology, which leads to cyclopentenone (−)-**5** in much higher yield and enantioselectivity than was previously achieved.

2. Results and discussion

2.1. Rearrangement studies

Our initial goal was to study, in greater detail, the rearrangement of pyranone **2** into cyclopentenone (±)-**3** in order to establish an asymmetric version. We screened reaction conditions using gas–liquid chromatography (GLC) (Tables 1 and 2), with the dual intention of achieving higher reactivity and some evidence for asymmetric induction using a chiral amine (Scheme 2).

Generally, stronger bases, such as triethylamine, diethylamine and diisopropylamine increased the rearrangement rate compared to weaker bases, such as 1-methylimidazole, 2,6-lutidine and pyridine, suggesting that base strength is an important factor affecting reactivity. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was also tested but led to decomposition from the onset. Interestingly, the most reactive amine was 4-diazabicyclo[2.2.2]octane (DABCO), and we note the trend of decreasing reactivity with increasing chain length for secondary amines. These observations together are consistent with the idea that both basicity and nucleophilicity play a significant role in determining reactivity. It was also observed that for the most reactive amines an isomeric product **4** is formed from (±)-**3**. In the case of diethylamine this resulted in a drop of the yield of (±)-**3** over time, being followed later by decomposition. This

Table 1
Effect of secondary and tertiary amines on the reactivity of the rearrangement of pyranone **2** to cyclopentenone (±)-**3**

Entry	Amine	(±)-**3** (%) per reaction time (min)		
		(20)	(60)	(120)
1	Diethylamine	53	45	27
2	Diisopropylamine	31	60	75
3	Dibutylamine	9	16	17
4	Dihexylamine	6	12	18
5	Dicyclohexylamine	21	45	66
6	Triethylamine	28	59	72
7	DABCO	56	64	58
8	DMAP	13	29	44
9	Pyridine	4	4	4
10	1-Methylimidazole	4	4	6
11	2,6-Lutidine	3	4	3
12	(−)-Sparteine	6	9	16
13	Quinine	29	54	58
14	Cinchonine	7	15	23
15	L-Cinchonidine	13	36	52

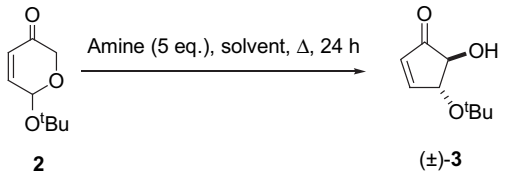
For all entries: **2** (0.29 M), amine (5 equiv) DMF, 70 °C; determined by GLC using *n*-decane as internal standard.

Table 2
Effect of solvent on the reactivity of the rearrangement of pyranone **2** to (±)-**3**

Entry	Solvent	(±)-**3** (%) per reaction time (h)		
		(2.5)	(5.5)	(25)
1	MeCN	44	87	26
2	THF	13	20	na
3	1,4-Dioxane	61	76	63
4	DMF	34	48	71
5	DMSO	40	66	88
6	HMPA	16	30	64
7	Triethylamine	7	13	na
8	Butyl acetate	6	6	21
9	*n*-Heptane	4	4	28
10	Toluene	4	4	29
11	tBuOH	69	81	70
12[a]	EtOH	34 (0.3)	62 (1)	51 (2)
13[a]	MeOH	14 (0.3)	20 (1)	17 (2)

For all entries: **2** (0.29 M), Et_3N (5 equiv), 70 °C; determined by GLC using *n*-decane as internal standard.

[a] Different sampling time is indicated in brackets.



2 (±)-3

Scheme 2. Studies on the rearrangement of pyranone **2** into *trans*-dioxygenated cyclopentenone (±)-**3** by screening different amine bases, solvents and temperatures.

effect varies with amine base, solvent and temperature, as discussed below (Table 3). (−)-Sparteine failed to exhibit acceptable reactivity but even those that did, such as quinine, quinidine, cinchonine, and L-cinchonidine failed to lead to the development of an asymmetric rearrangement owing to poor ee values (ee <6%, Table S1 of Supplementary data).

Table 3
Yield and ratio of (±)-**3** and **4** with selected reaction conditions

Entry	Solvent	Temp (°C)	Base (equiv)	Reaction time (h)	Yield (±)-**3**, **4**[a]	Ratio (±)-**3**/**4**[b]
1[c]	DMF	80	Et_3N (5)	24	74	91:9
2[c]	DMSO	80	Et_3N (5)	24	22	49:51
3[c]	DMA	80	Et_3N (5)	24	62	97:3
4[c]	MeCN	80	Et_3N (5)	24	45	15:85
5[c]	MeOH	80	Et_3N (5)	24	22	0:100
6[c]	EtOH	80	Et_3N (5)	24	65	0:100
7[c]	^{t}BuOH	80	Et_3N (5)	48	59	21:79
8[c]	^{t}BuOH	80	Et_3N (5)	5	83	78:22
9[d]	^{t}BuOH	50	DABCO (0.1)	48	77	96:4
10[e]	^{t}BuOH	50	DABCO (0.15)	24	85	97:3
11[e]	^{t}BuOH	50	DABCO (0.2)	24	82	98:2

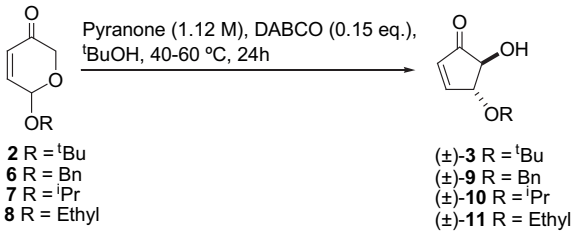
[a] Isolated yield by flash chromatography.
[b] Ratio of (±)-**3**/**4** determined by ^{1}H NMR.
[c] Reactions were performed using **2** (0.29 M).
[d] Reaction was performed using **2** (0.58 M).
[e] Reactions were performed using **2** (1.16 M).

In order to optimise the rearrangement towards the production of **3** we examined the effect of the solvent on the yield of **3** (Table 2) and the **3**/**4** ratio (Table 3).

The rearrangement is slow in apolar and weakly polar solvents, but there is considerable variation in polar solvents with the highest reactivity observed for alcohols, albeit that this reactivity was also accompanied by a propensity for the production of **4** followed by decomposition. We then focused on a smaller selection of promising polar solvents with a range of amine bases and temperatures in order to suppress the formation of **4** (Table 3).

Entry 1 stands as the reference following the previously reported method,[16] which also affords some of the thermodynamically favoured isomer **4**. Although DMSO and DMA (entries 2 and 3) initially showed promise, it was later found that when the temperature was lowered to 40–50 °C in order to minimize formation of **4**, the rearrangement rate dropped significantly compared to *tert*-butanol. For methanol and ethanol the product **4** is dominant and the overall yield is lower due to decomposition (entries 5 and 6). For *tert*-butanol we observed that (±)-**3** was formed first before being converted into **4** or undergoing decomposition (entries 7 and 8). Having considered that conversion into **4** was being accelerated by using higher temperatures and base equivalents, we decided to significantly lower both of these conditions in order to achieve higher selectivity towards (±)-**3**. We also decided to use the most reactive amine, DABCO, to afford higher yields for (±)-**3** under these milder conditions. Thus, improved yields and selectivity towards (±)-**3** were obtained by altering the reaction time, lowering the temperature and using DABCO in catalytic quantities as a base in *tert*-butanol. With these optimized conditions we have achieved an effective rearrangement with DABCO present in 15–20 mol % in *tert*-butanol at a milder temperature of 50 °C with good reproducibility giving high isolated yields (82–85%) and excellent ratios of the desired product (entries 9–11).

We also studied the application of this methodology to substrates with different alkyl protecting groups (Scheme 3 and Table 4). The significant variation in yield unfortunately illustrates the need of further careful optimisation for each case.



2 R = ^{t}Bu
6 R = Bn
7 R = ^{i}Pr
8 R = Ethyl

(±)-**3** R = ^{t}Bu
(±)-**9** R = Bn
(±)-**10** R = ^{i}Pr
(±)-**11** R = Ethyl

Scheme 3. Rearrangement of a selection of pyranones into racemic *trans*-dioxygenated cyclopentenones using optimized rearrangement method.

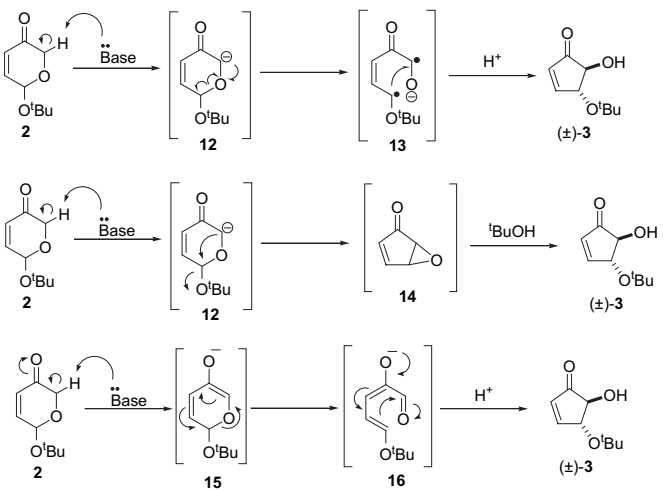
Table 4
Yields for isolated products obtained using conditions optimized for (±)-**3**

Entry	Starting material	Temperature (°C)	Product[a]	Yield[b] (%)
1	2	50	(±)-**3**	85
2	6	40	(±)-**9**	30
3	7	60	(±)-**10**	62
4	8	50	(±)-**11**	14

[a] Structure confirmed by ^{1}H and ^{13}C NMR.
[b] Pyranone (1.12 M), DABCO (0.15 equiv), *tert*-butanol, 40–60 °C. Yields obtained from product isolated by column chromatography.

Previously we had proposed that the mechanism for this rearrangement could either be based on a 1,2-Wittig rearrangement involving biradical **13**, cyclization to give epoxide **14** followed by nucleophilic ring opening or cyclization of an intermediate **16** formed by electrocyclic ring opening of an enol (Scheme 4).[48]

The possibility that epoxide **14** was an intermediate was discounted after it was shown that the reaction could proceed in methanol without methoxide incorporation into the product.[48,49] We have also undertaken the rearrangement in the absence and presence of a radical trap, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to evaluate the possible involvement of a radical intermediate (Fig. 1). The presence of this radical trap has almost no influence on the reaction rate, thus making it highly unlikely that radical species would be involved.



Scheme 4. Possible mechanisms involved in the pyranone rearrangement. Top: biradical **13** involved in a possible 1,2-Wittig rearrangement. Centre: formation of epoxide **14** followed by nucleophilic attack to afford a dioxygenated cyclopentenone Bottom: cyclization of intermediate **16** formed by electrocyclic ring opening of an enol.[48]

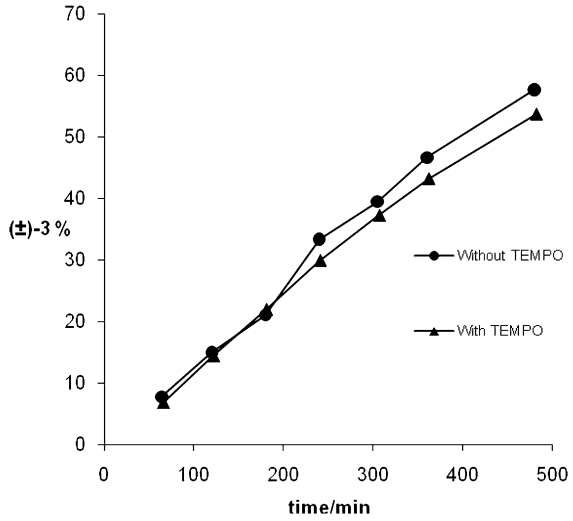


Fig. 1. Rearrangement of pyranone **2** (0.15 M) to (±)-**3** with DABCO (2.5 equiv) in the absence and presence of TEMPO (1 equiv) in DMA at 40 °C; conversion determined by GLC using *n*-decane as an internal standard.

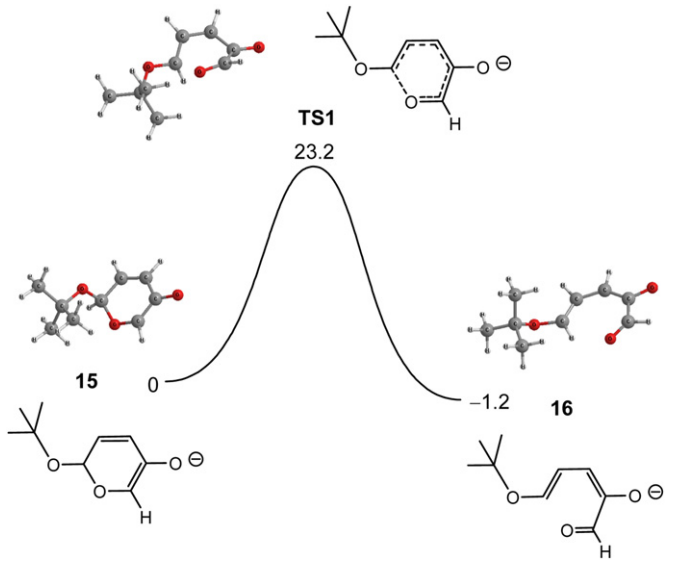


Fig. 2. Energy profile calculated (PBE1PBE) for the formation of **16** through ring opening of **15**. The minima and the transition state were optimized and the energy values (kcal/mol) are referenced to **15**.

The most likely mechanism involves electrocyclic ring opening from an enol (Scheme 4) and such an ionic mechanism would likely be enhanced by enol stabilization with increasingly polar and protic solvents, which is consistent with our observations. Notably, a very similar mechanism has been proposed for the diastereoselective synthesis of *trans* diamino cyclopentenones reported by Li and Batey.[52] Deuteration studies showed that base catalysis is essential for the rearrangement, which takes place without observing any intermediates (Tables S32–S38, Supplementary data). Moreover the failure of α-methylated pyranone **20** to undergo rearrangement under the optimized conditions is also consistent with the reduced electrophilicity of a postulated ketone intermediate derived from **20** (Scheme 5).

DFT calculations[53] were used to predict the energies of the two intermediates **15** and **16** in the 6 π-electron electrocyclic ring opening, taking place through a disrotatory transition state (**TS1**) in accordance with the Woodward–Hoffmann rules (Fig. 2).[54] The stability of these two intermediates was found to be similar (within 1.2 kcal/mol). In contrast the energy barrier for the ring opening process was calculated at 23.2 kcal/mol, which although high is accessible under the experimental conditions (Table 3).

The formation of the cyclopentenone ring from intermediate **16** was investigated for both the *cis* and *trans* products pathways. The cis pathway leads to alkoxide **21**$^-$, which upon protonation yields the cis isomer of cyclopentenone (**21**) (Fig. 3).

The mechanism obtained for the formation of **21**$^-$ from **16** comprises two steps. In the first step, there is rotation of the formyl group with a concurrent rearrangement of the C_5 chain that goes from practically planar in **16** to a helicoidal geometry in intermediate **I1**, where the relevant groups are in the relative positions needed for the final step. Finally, C_5 ring closure occurs and the two *O*-substituents are locked on the same side of the ring plane in the product, **21**$^-$. Both steps are quite accessible with calculated energy barriers of 4.2 and 15.3 kcal/mol.

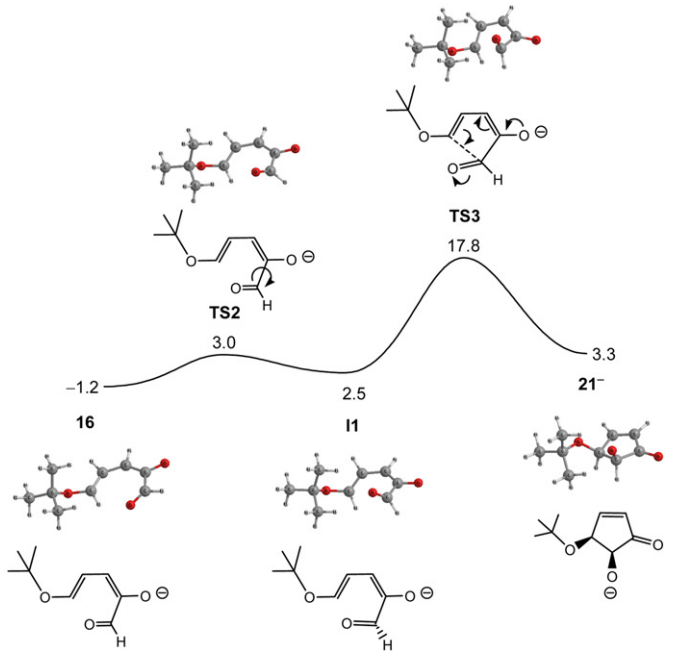
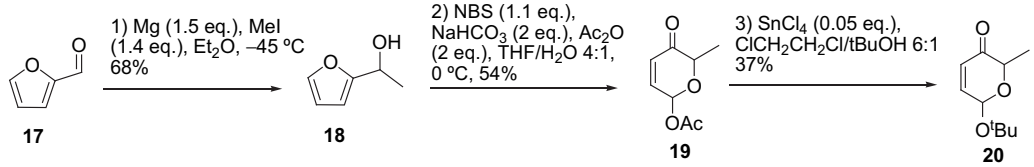


Fig. 3. Energy profile calculated (PBE1PBE) for formation of *cis* dioxygenated cyclopentenone **21**$^-$ from **16**. The minima and the transition state were optimized and the energy values (kcal/mol) are referenced to **15**.

The energy profile in Fig. 4 represents ring closure from intermediate **16**, resulting in the formation of *trans* alkoxide **3**$^-$.

The mechanism obtained for the formation of alkoxide **3**$^-$ involves three steps. In the first one, there is rotation of the formyl group that goes from a cis arrangement relative to the C_5 chain, in



Scheme 5. Synthetic route to pyranone **20**, methylated in the alpha position, via an adapted procedure.[16]

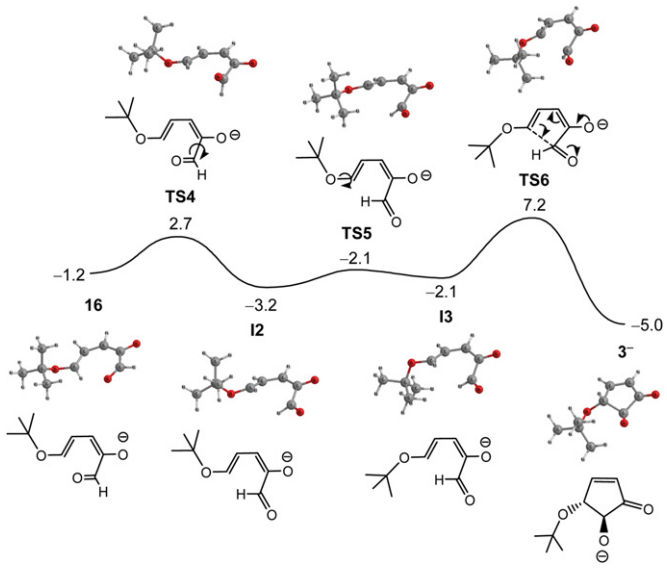
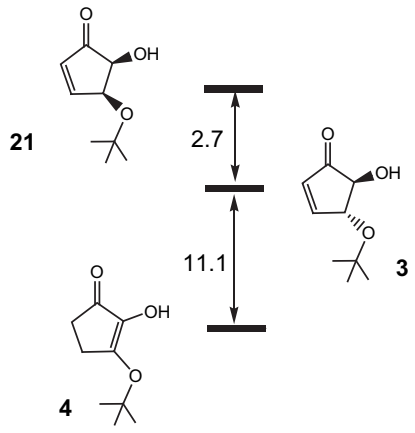


Fig. 4. Energy profile calculated (PBE1PBE) for formation of *trans*-dioxygenated cyclopentenone **3**$^-$ from **16**. The minima and the transition state were optimized and the energy values (kcal/mol) are referenced to **15**.

16, to a trans orientation in intermediate **I2**. At the same time the C_5 chain changes from an almost planar geometry to a helicoidal arrangement. The free energy barrier calculated for the first step is low (3.9 kcal/mol), and the step is thermodynamically favourable (ΔE=−2.0 kcal/mol). The second step, from **I2** to **I3**, corresponds to a simple rotation around the C–O^{t}Bu bond and has a very low free energy barrier (0.9 kcal/mol). The energy barrier calculated for the final step is rather low (9.3 kcal/mol) and the process is favourable (2.9 kcal/mol). In a similar way to the proposed mechanism of formation of **21**$^-$, the step leading to **3**$^-$ can be viewed as the result of a conrotatory movement of the terminal groups in the carbon chain of **I3**, following the Woodward–Hoffmann rules for a 4 electron π-system.

Alkoxide **3**$^-$ is both the thermodynamic and the kinetic product of the reaction. In fact, **3**$^-$ is more stable than **21**$^-$ by 8.3 kcal/mol and, in addition, the highest energy barrier involved in the formation of **3**$^-$, from intermediate **16**, is 9.3 kcal/mol, compared to 15.3 kcal/mol in the case of the **21**$^-$. In both cases, those activation energy values are associated with the last step of the corresponding mechanism, that is, C–C bond formation effecting C_5 ring closure, and thus, the differences observed should be related to steric repulsion between C_5 ring substituents. Interestingly, isomer **4** is calculated to be more stable than **3** by 11.1 kcal/mol (Scheme 6). This is in good accordance with the experimental observations,



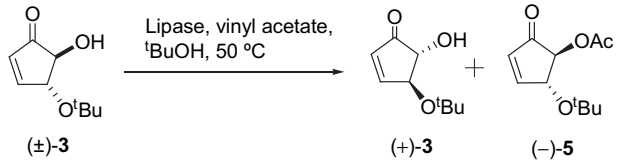
Scheme 6. Stability differences (kcal/mol) between isomers of cyclopentenone **3**.

namely the formation of the undesirable reaction product **4**, with prolonged reaction times and/or stronger bases.

In summary, ring opening, from enolate **15** to intermediate **16**, corresponds to the rate-limiting step in the calculated mechanism. However, the activation energy associated with that step (23.2 kcal/mol) is quite accessible for the temperature and the reaction times used in the experimental conditions (Table 3). The lower energy barrier for ring closure leading to alkoxide **3**$^-$ accounts for the observed diastereoselectivity. Although we carried out further work in which we tried to gain evidence for intermediates via NMR, MS and FTIR, we failed to observe any intermediates, such as **15** or **16**. This reinforces the idea that the rate-limiting step of the entire process is the initial deprotonation (see Supplementary data).

2.2. Studies on resolution

With an improved rearrangement protocol in hand we proceeded to study the coupling of the rearrangement with an enzymatic resolution. Our prior enzymatic resolution protocol used significant excess of immobilized enzyme (5 mass equiv) and acylating agent (vinyl acetate 87 equiv) and a prolonged reaction time of 7 days.[50] Furthermore, previous results suggested that alkaline conditions could induce racemization of cyclopentenone (±)-**3**.[50] Thus, we undertook studies towards the establishment of an improved protocol for a one-pot rearrangement, DKR process. We began by screening a series of soluble non-immobilized enzymes to identify a more active lipase for the acylation of isolated (±)-**3** to (−)-**5** (Scheme 7, Table 5).



Scheme 7. Lipase-catalyzed resolution of isolated cyclopentenone (±)-**3** via enzymatic acylation.

Table 5
Lipase screening for enzyme catalyzed acylation of (±)-**3** over 10 days

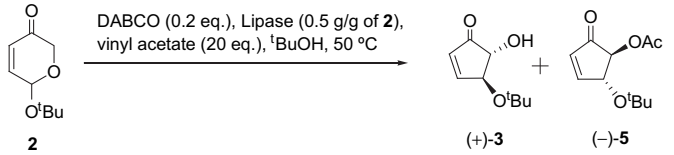
Entry	Lipase	(−)-**5** (%)	(−)-**5** ee (%)
1	AK Amano 20	42	97
2	PS Amano IM	29	97
3	PS Amano SD	22	95
4	AS Amano	5	81
5	AYS Amano	1	23
6	Novozyme	3	76

For all entries: (±)-**3** (0.12 M), lipase (0.56 mg/mg of (±)-**3**), vinyl acetate (20 equiv), *tert*-butanol, 50 °C, 10 days; determined by GLC using *n*-dodecane as an internal standard.

Our previously reported procedure used lipase PS Amano SD[50] but we found that all lipases tested other than AYS Amano showed higher activity with reasonable to good enantioselectivity, particularly lipases AK Amano 20 and PS Amano IM. We chose to focus our further studies on lipase AK Amano 20 since it showed the highest activity and enantioselectivity. We also observed that it is possible to use non-immobilized lipases as they were shown to work within these conditions. Since we were interested in conducting both the rearrangement and the enzymatic resolution within the same step, we used *tert*-butanol as a solvent. Though in principle competitive acylation could take place, we hoped that it would be unlikely given that *tert*-butanol is a tertiary alcohol. Indeed we have not observed any competitive acylation. While

lipases have been traditionally used in predominantly apolar or weakly polar organic solvents, we felt this would be an excellent opportunity to test and extend lipase use to more polar solvents.

Next, we added the enzyme and vinyl acetate directly to the mixture of pyranone **2** and DABCO under optimized rearrangement conditions (Scheme 8), with the objective of conducting both the rearrangement and the enzymatic resolution within the same step (Fig. 5).



Scheme 8. Simultaneous rearrangement and lipase resolution for conversion of **2** into (−)-**5**.

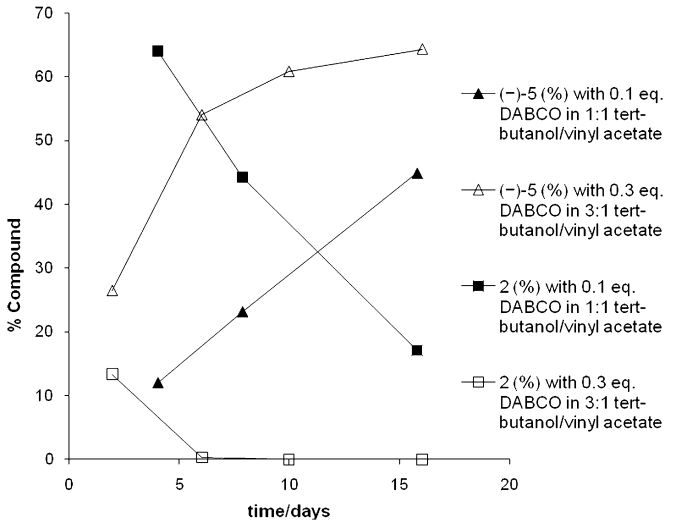


Fig. 5. Simultaneous rearrangement and lipase resolution of **2** into (−)-**5**: **2** (0.29 M), DABCO, lipase (0.5 mg/mg of **2**), vinyl acetate (20 equiv of vinyl acetate for filled symbols data, 5 equiv for empty symbols data), *tert*-butanol, 50 °C; determined by GLC using *n*-dodecane as an internal standard; ee of (−)-**5** after 16 days: ▲ ee 84%, Δ ee 77%.

With a 1:1 (v/v) ratio of *tert*-butanol/vinyl acetate using 0.1 equiv of DABCO we observed a lower rate of acylation than previously reported[51] with 45% of acetylated product (−)-**5** isolated after 15 days, due to a slower rate of rearrangement. The reduced rate of rearrangement may be due to one of two possible causes: protonation of DABCO by acetic acid generated from vinyl acetate hydrolysis; or the decrease in the medium polarity caused by the presence of vinyl acetate. In fact, by increasing the amount of DABCO and decreasing the amount of vinyl acetate we achieved a better reaction rate for the rearrangement, with much faster consumption of **2** and an improved yield of 64% for (−)-**5** after 15 days. In spite of this improvement, we continued to observe the presence of pyranone **2** after 5 days. This fact combined with the modest yield and the poor enantioselectivity of the acylation step convinced us that the conditions for the rearrangement and the lipase-catalyzed acylation were partially incompatible with each other. It was also observed that ee for **3** under these conditions after 15 days was very low, standing at 4%, which clearly indicated that racemization of (+)-**3** was taking place. This prompted us to investigate the conditions for racemization of **3** (Table 6).

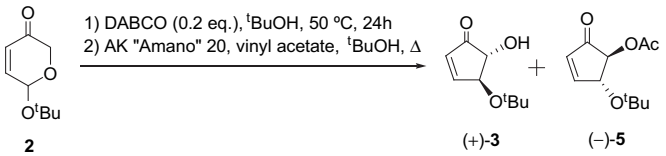
Table 6
Enantiomeric excess for a mixture of enantiomerically enriched (+)-**3** and (−)-**5** submitted to various conditions

Entry	Conditions	Time (days)	Initial (+)-**3** ee (%)	Final (+)-**3** ee (%)	Initial (−)-**5** ee (%)	Final (−)-**5** ee (%)
1[a]	tBuOH, room temperature	3	45	27	94	91
2[a]	tBuOH, 50 °C	3	45	21	94	91
3[a]	tBuOH, 50 °C, DABCO 0.2 equiv	4	45	43	94	94
4[a]	tBuOH, 50 °C, DABCO 0.4 equiv	4	45	41	94	93
5[a]	tBuOH, 50 °C, HCl pH 1–2	4	45	6	94	92
6[b]	tBuOH, 50 °C, AK Amano 20	1	9	1	88	81
7[b]	tBuOH, 50 °C, silica gel 60	4	9	2	88	80

Enantiomeric excess determined by GLC in a chiral column.
[a] Started with mixture of (±)-**3** (45% yield) and (−)-**5** (50% yield) obtained from lipase acylation of (±)-**3** (lipase PS Amano SD immobilized in Celite (5 mg/mg of (±)-**3**), vinyl acetate (87 equiv), 40 °C, 12 days).
[b] Started with same mixture after being kept at −5 °C for 14 days.

Racemization of (+)-**3** is observed simply by allowing it to stand in *tert*-butanol or by heating (entries 1 and 2). On the other hand, DABCO in small amounts suppressed racemization (entries 3 and 4), thus ruling out DABCO induced racemisation. Racemization was induced effectively by acidification to pH 1–2 (entry 5), but this was later shown to be detrimental to lipase activity (Fig. S1 of Supplementary data). The presence of lipase AK Amano 20 resulted in remarkable racemization of (+)-**3** (entry 6), suggesting racemization is related to the activity of the enzyme either directly or indirectly (via acetic acid produced by vinyl acetate hydrolysis). Addition of silica gel 60 to the mixture was demonstrated to induce racemization of (+)-**3** (entry 7). The use of silica gel 60 improved racemization of (±)-**3** by keeping its ee in the 5–14% range when using the sequential one-pot method discussed later in this paper (Fig. S2 of Supplementary data). Also, the acetylated cyclopentenone (−)-**5** is generally much more resistant to racemization than (±)-**3**. No *cis* products were ever isolated from reactions using the simultaneous method of rearrangement and lipase.

With conditions for racemization of (+)-**3** at hand, we studied the lipase-catalyzed acylation in order to increase the lipase activity. Given our previous difficulties with the simultaneous procedure (Scheme 8), we decided to study a one-pot, sequential procedure were the rearrangement is carried out first over 24 h, after which time a sufficient amount of acetic acid was added to the reaction mixture for neutralization, followed by the lipase, silica gel 60 and vinyl acetate (Scheme 9).



Scheme 9. One-pot, sequential methodology for conversion of **2** into (−)-**5** via rearrangement followed by dynamic kinetic resolution.

We studied this sequential, one-pot procedure by variation of the acylating agent amount (5–20 equiv) and pH (3–9) and found that there was no appreciable impact on the reaction as yields of 45–53% and ees of 67–81% were observed for (−)-**5** (Figs. S1–S3 of Supplementary data). However we noted that the reaction tended to reach a plateau after 24 h, which led us to study possible enzyme inhibition taking place (Table 7).

Table 7
Different experiments varying lipase use and initial amount of (−)-**5** for the lipase resolution of (±)-**3** after rearrangement from **2**

Entry	Conditions	(−)-**5**% per reaction time (days)			
		(1)	(3)	(5)	(7)
1	Lipase (1 mg/mg of **2**)	43	47	51	53
2	Lipase (2 mg/mg of **2**)	43	43	45	48
3[a]	Lipase previously used once (1 mg/mg of **2**)	5	22	31	Na
4	Lipase renewed with every sample (1 mg/mg of **2**)	42	45	44	45
5[b]	Lipase (1 mg/mg of **2**), started with 65% of (−)-**5**	74	72	73	78

For all entries: **2** (1.16 M), DABCO (0.2 equiv), *tert*-butanol, 50 °C, 24 h; then neutralized with acetic acid solution, AK Amano 20, vinyl acetate (10 equiv unless otherwise stated), 50 °C; determined by GLC using *n*-dodecane as an internal standard.

[a] Reuses enzyme from another equivalent experiment.

[b] Has initial amount of (−)-**5** indicated as a molar percentage of the initial amount of **2**.

There is evidence of enzyme deactivation regardless of the amount of lipase used or lipase renewal once (−)-**5** yield is greater than 40%. We believe (−)-**5** might inhibit the enzyme in some way and thus we changed the conditions by employing a higher temperature and a solvent mixture with greater polarity in order to favour release of (−)-**5** from the enzyme. We also added silica gel to aid racemisation of **3**. The results of these combined efforts applied to our one-pot methodology were successful in increasing the yield and optical purity of (−)-**5** finally achieving 81% yield and 95% ee with 6:1 *tert*-butanol/vinyl acetate at 60 °C (Fig. 6).

We also examined the effect of recycling the enzyme, having observed that there is a slight drop in yield and a more significant drop in ee particularly after the second cycle (Fig. 7).

Having found optimized conditions for both the rearrangement and the enzymatic acylation, we synthesized (−)-**5** from pyranone **2** with an isolated high yield of 81% for (−)-**5** with excellent ee of 96%.

We then also evaluated other substrates with some success, albeit with diminished efficiency (Scheme 10, Table 8). It is conceivable that yields and optical purities for different substrates might be improved with further optimization of rearrangement and resolution conditions.

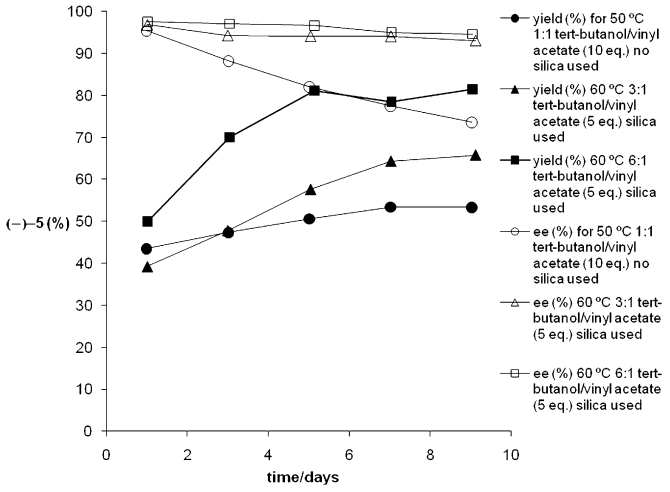


Fig. 6. Effect of silica gel 60, temperature and solvent mixture ratio on the yield of (−)-**5** in the sequential, one-pot procedure: **2** (1.16 M), DABCO (0.2 equiv), *tert*-butanol, 50 °C, 24 h, then neutralized with acetic acid solution, AK Amano 20 (1 mg/mg of **2**), vinyl acetate, silica gel 60 (5 mg/mg of lipase used unless otherwise stated), further addition of *tert*-butanol to correct solvent mixture ratio of *tert*-butanol/vinyl acetate (v/v) to displayed value; determined by GLC using *n*-dodecane as an internal standard.

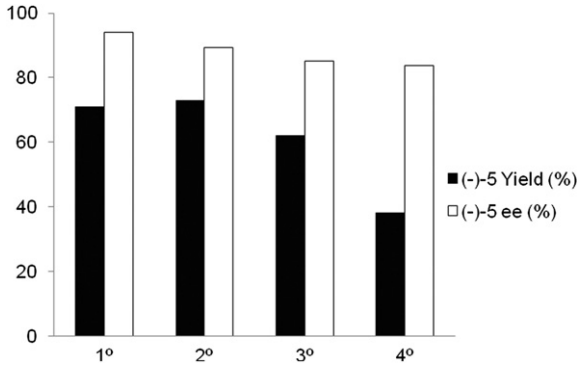
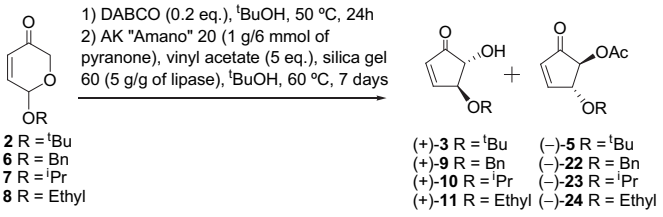


Fig. 7. Yield and ee of (−)-**5** for enzyme batch reuse for four cycles: **2** (1.16 M), DABCO (0.2 equiv), *tert*-butanol, 50 °C, 24 h, then neutralized with acetic acid solution, AK Amano 20 (1 mg/mg of **2**), vinyl acetate (5 equiv), silica gel 60 (5 mg/mg of lipase), further addition of *tert*-butanol to correct solvent mixture ratio to 6:1 *tert*-butanol/vinyl acetate v/v, 60 °C; determined by GLC using *n*-dodecane as an internal standard.



Scheme 10. Single pot methodology for the asymmetric synthesis of (−)-**5** and analogues via rearrangement followed by dynamic kinetic resolution.

Table 8
Yield and ee for isolated products obtained by optimized single pot procedure with rearrangement followed by dynamic kinetic resolution

	Starting material	Product	Yield (%)	ee (%)
1	**2**	(−)-**5**	81	96
2	**6**	(−)-**22**	48	80
3	**7**	(−)-**23**	59	87
4	**8**	(−)-**24**	49	73

Pyranone (1.16 M), DABCO (0.2 equiv), *tert*-butanol, 50 °C, 24 h, then neutralized with acetic acid solution, AK Amano 20 (1 mg/0.006 mmol of pyranone), vinyl acetate (5 equiv), silica gel 60 (5 mg/mg of AK Amano 20), further addition of *tert*-butanol to correct solvent mixture ratio to 6:1 *tert*-butanol/vinyl acetate, 60 °C. Yields obtained from isolated product by column chromatography. Enantiomeric excess determined by GLC using *n*-dodecane as an internal standard.

3. Conclusions

In conclusion, we have studied and optimised the rearrangement of a pyranone **2** into a dioxygenated cyclopentenone (±)-**3**. We have screened amine bases, solvents and temperature extensively to identify more reactive amines and milder conditions for the rearrangement, while avoiding undesirable formation of isomer **4**. The enhanced rate observed in protic solvents was used to our advantage to minimize formation of undesirable isomer **4** by reduction of the reaction temperature and quantity of base.

The enhanced reaction rate in protic solvents, requirement for basic catalysis and other observations are consistent with a mechanism based on cyclization of an intermediate formed through electrocyclic ring opening of an enolate **15**. The mechanism is supported by DFT calculations, which indicate that, once enolate **15** is formed, ring opening corresponds to the most energetically demanding step and that *trans* cyclopentenone (±)-**3** is both the thermodynamic and kinetic product, which accounts for the observed diastereoselectivity.

Our milder conditions for this rearrangement allowed for telescoping this transformation through the dynamic kinetic resolution to afford enantiomerically enriched acylated cyclopentenone (−)-**5**. Thus we developed a one-pot, sequential method whereupon the rearrangement is carried out first, followed by a lipase-catalyzed acylation. AK Amano 20 was the best enzyme at elevated temperature using a polar solvent mixture and silica gel. Under these conditions the target cyclopentenone (−)-**5** could be isolated in high yield and excellent enantiomeric purity. We applied this methodology to other pyranone analogues albeit with slightly poorer yields and optical purities. To the best of our knowledge this is the first case of a dynamic kinetic resolution as an asymmetric synthesis strategy for enantiomerically enriched *trans*-dioxygenated cyclopentenone.

4. Experimental

4.1. General

The preparation of compounds (±)-**3**, **2**, (−)-**5** and (±)-**9** was described previously,[16] as well that of compound **4**,[48] and compounds **18**, **19** and **20**.[49] New procedures for the preparation of compounds (±)-**3**, (−)-**5**, **7**, **8**, (±)-**10**, (±)-**11**, **18**, **19**, **20**, (−)-**22**, (−)-**23** and (−)-**24** are presented in the Supplementary data.

*4.1.1. (1S,2R)-2-tert-butoxy-5-oxocyclopent-3-enyl acetate (−)-**5** (by sequential, one-pot procedure).* To a solution of 6-*tert*-butoxy-2*H*-pyran-3(6*H*)-one **2** (obtained by reported procedure[16]) (400 mg, 2.35 mmol) in *tert*-butanol (2 mL) was added DABCO (40 mg, 0.357 mmol, 0.15 equiv). The solution was stirred at 50 °C for 24 h. After cooling the solution, an acetic acid solution in *tert*-butanol (0.2 mL, 0.1 g/mL) was added to neutralize DABCO the reaction. Next, vinyl acetate (1.08 mL, 11.7 mmol, 5 equiv), lipase AK Amano 20 (400 mg), silica gel C60 (2 g, 0.04–0.06 mm) and *tert*-butanol (3.8 mL) were added. The mixture was stirred in a closed Teflon vessel at 60 °C for 7 days. Afterwards, the mixture was cooled down to room temperature, filtered and the filter cake was washed with dichloromethane (20 mL). An acetic acid/sodium acetate buffer solution at pH 5 (10 mL) was added to the filtrate and stirred. The organic phase was separated and the aqueous phase was further extracted with dichloromethane (2×20 mL). The combined organic solution was dried (Na_2SO_4), filtered and concentrated under reduced pressure to yield a yellow oil, which was purified by flash chromatography on silica with dichloromethane/ethyl acetate (20:1 v/v) to afford (−)-**5** as a pale-yellow low melting point solid (402.1 mg, 81%, ee 95%) and (+)-**3** and **4** (38 mg, 9.6%, ee of (+)-**3** 4.4% in 70:40 ratio (determined by GLC)) as a yellow low melting point solid. δ_H (300 MHz, $CDCl_3$) 1.24 (9H, s), 2.15 (3H, s), 4.83 (1H, m), 5.01 (1H, d, J=2.7 Hz), 6.26 (1H, dd, J=6.2, 1.5 Hz), 7.31 (1H, dd, J=6.2, 2.1 Hz); δ_C (75 MHz, $CDCl_3$) 20.6, 28.1, 73.8, 75.2, 81.0, 132.6, 160.3, 170.0, 199.0; HRMS (EI) $[M]^+$ found 212.10482, $C_{11}H_{16}O_4$ requires 212.10431.

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Supplementary data

Spectral data and experimental procedures for all new compounds. Representative chromatograms of reaction samples and of racemic and enantiomerically enriched compounds. Spectral data for deuteration and mass spectrometry studies. Additional table and graphs for rearrangement and resolution studies. Computational details and associated reference list. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.02.018. These data include MOL files and InChIKeys of the most important compounds described in this article.

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