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Asymmetric synthesis of pent-3-yl (*R*)-6-methyl-cyclohex-1-ene carboxylate

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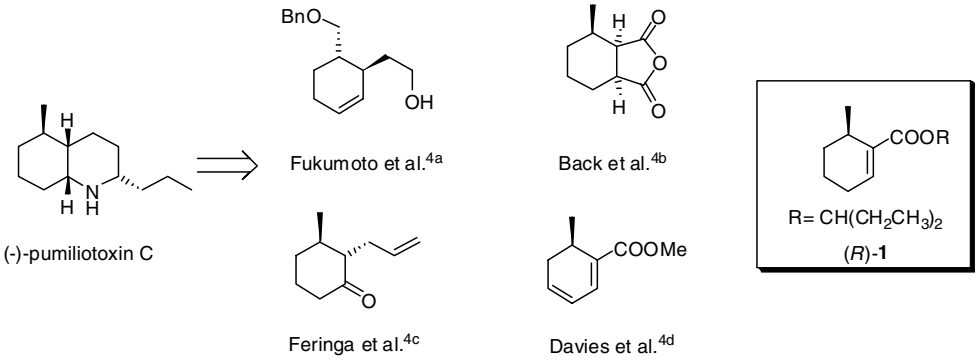
Dedicated with respect and affection to Professor J. G. Urones on the occasion of his 65th birthday

Abstract—An expeditious asymmetric synthesis of pent-3-yl (*R*)-6-methyl-cyclohex-1-enecarboxylate has been achieved in four steps in 42% overall yield employing as the key step a domino reaction initiated by a highly diastereoselective lithium amide 1,4-conjugate addition to a nona-2,7-diendioic diester followed by a 6-*exo-trig* cyclisation of the thus formed enolate. Cope elimination protocol of the cyclic adduct affords, depending on the lithium amide used, the corresponding nitro-compound or the expected cyclohexene derivative. The methyl group attached to the cyclohexane ring is achieved by selective ester hydrolysis and subsequent Barton decarboxylation.

1. Introduction

The methodologies and strategies for the stereoselective construction of substituted cyclohexane rings are very powerful synthetic tools since such rings are incorporated in many naturally occurring products. Representative examples are: morphine[1] with a cyclohexane ring *trans*,*trans*-trisubstituted and luciduline[2] where the ring is *cis*,*cis*-trisubstituted. Pumiliotoxin C with a *cis*-decahydroquinoline skeleton, first isolated from *Dendrobates pumilio*, is one of the most prominent members among the alkaloids isolated from *Dendrobates* spp. (poison dart frog).[3] An impressive effort has been devoted to the asymmetric synthesis because of its structure, a *cis*-fused perhydroquinoline skeleton featuring four stereogenic centres.[4] In Scheme 1 are shown some of the cyclohexanic derivatives used recently in the asymmetric synthesis of pumiliotoxin C, and the related compound pent-3-yl (*R*)-6-methyl-cyclo-



Scheme 1.

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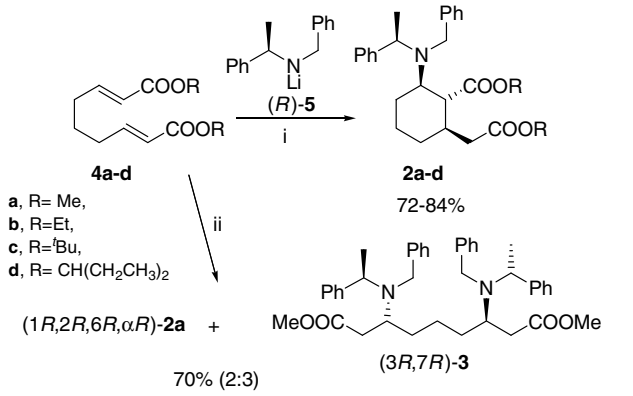
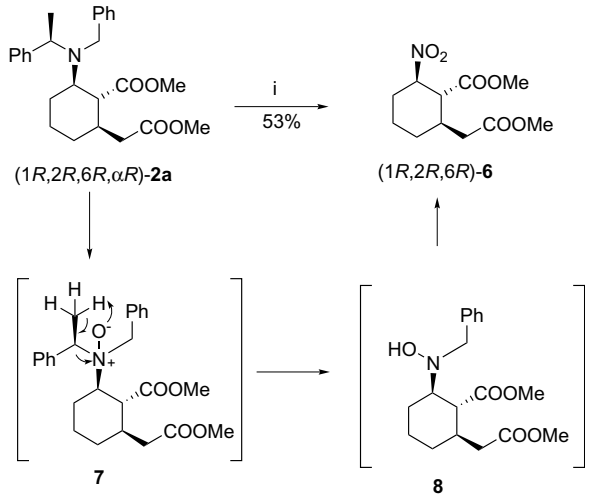


Scheme 2. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide [(*R*)-**5**, 1.6 equiv, THF, −78 °C]; (ii) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide [(*R*)-**5**, 12 equiv, THF, −78 °C].



Scheme 3. Reagents and conditions: (i) *m*-CPBA (4 equiv), 3 days.

hex-1-enecarboxylate ester (*R*)-**1**, whose synthesis is reported here.

We have previously demonstrated the asymmetric synthesis of the cyclic monoaddition and open chain diaddition products **2** and **3** from (*E*,*E*)-nona-2,7-diendioate **4a**–**d** (Scheme 2).[5] The cyclic adduct **2** is obtained by addition of homochiral lithium *N*-benzyl-*N*-α-methylbenzylamide (*R*)-**5** (1.6 equiv) via a domino[6] reaction initiated in an asymmetric conjugate addition followed by an intramolecular 6-*exo*-*trig* cyclisation of the enolate formed with the remaining α,β-unsaturated ester. On the other hand, addition of (*E*,*E*)-deca-2,8-diendioate to an excess of lithium amide gave the diaddition adduct as the only isolated product.[5] However addition of methyl (*E*,*E*)-nona-2,7-diendioate **4a** to an excess of amide (*R*)-**5** (12 equiv) gave the diaddition adduct (3*R*,7*R*)-**3** and cyclic **2a** in a 3:2 ratio. Nevertheless, compound (3*R*,7*R*)-**3**, has been obtained completely selectively in a strategy based on (*Z*,*E*)-nona-2,7-diendioate by reaction with (*R*)-**5** producing the β,γ-unsaturated monoaddition product, which by base catalysed isomerisation to the α,β-unsaturated ester and new addition, yields (3*R*,7*R*)-**3**. In this way, *meso*-**3** could be obtained as well when (*S*)-**5** is added to the monoaddition derivative.[5a] This sequential strategy allows the stereochemical control of the two new stereogenic centres.

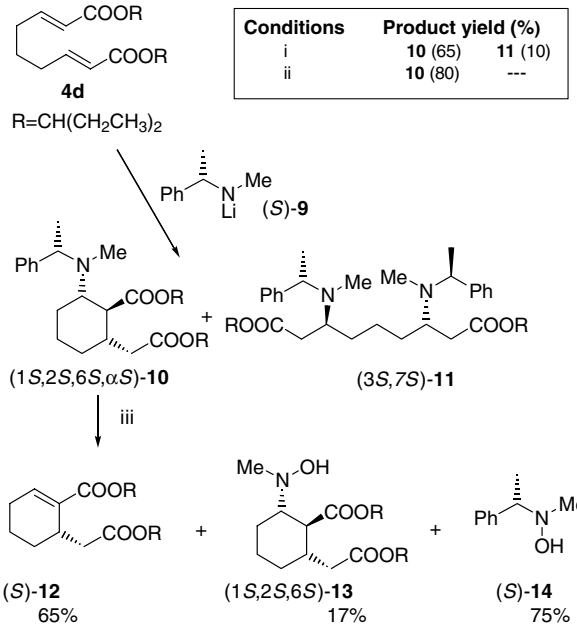
In order to demonstrate further the versatility of this lithium methodology by generating chiral methyl cyclohexane derivatives, a study with sequential amine elimination, selective ester hydrolysis and Barton's decarboxylation on **4d** was undertaken.

2. Results and discussion

We envisaged that Cope elimination between H-1 and the amino group in the cyclohexane compound (1*R*,2*R*,6*R*,α*R*)-**2a** (Scheme 3) would provide the alkene derivative in accordance with previous observations in the cyclopentane series.[7] However, treatment of compound (1*R*,2*R*,6*R*,α*R*)-**2a** with *m*-chloroperbenzoic acid over a long period of time generated, the nitro derivative (1*R*,2*R*,6*R*)-**6**, in 53% isolated yield[8] as a single diastereoisomer. Presumably with all groups especially the large amino group equatorial in the trisubstituted chair conformation of the cyclohexane, in the *N*-oxide initially formed **7**. It is difficult to adopt the *syn*-periplanar conformation required to generate a cyclohexene derivative, favouring Cope elimination with a hydrogen from the α-methyl group yielding styrene and the hydroxy-amine **8**. Subsequent dehydration and further oxidation would produce an *N*-oxide oxaziridine derivative, rearrangement of which would give benzaldehyde and a nitroso compound, which after additional oxidation would account for the production of (1*R*,2*R*,6*R*)-**6**.[9] Due to this unexpected result[10] and the versatility of the nitro group that can, for example, be transformed to carbonyl functionality through a Nef reaction,[11] further investigations on the scope of this reaction are currently being performed in our laboratory.

The less bulky chiral lithium (*S*)-*N*-methyl-*N*-α-methylbenzylamide (*S*)-**9**, has been demonstrated previously to favour Cope eliminations.[12] Addition of dipent-3-yl (*E*,*E*)-nona-2,7-diendioate **4d** to (*S*)-**9** (1.8 equiv) at −78 °C followed by quenching with saturated aqueous ammonium chloride gave the readily separable, by flash chromatography (silica; 5% EtOAc in hexane), cyclohexane adduct (1*S*,2*S*,6*S*,α*S*)-**10**,[8] $[\alpha]_D^{20} = -2.5$ (*c* 1.4, $CHCl_3$), together with the diaddition adduct (3*S*,7*S*)-**11** in 65% and 10% isolated yields, respectively (Scheme 4). This result suggests that the ratio of adducts obtained, depends not only on the amount but also on the size of the lithium amide used. Thus slow addition of (*S*)-**9** to **4d** at −78 °C provided (1*S*,2*S*,6*S*,α*S*)-**10** as the only isolated compound in 80% yield.

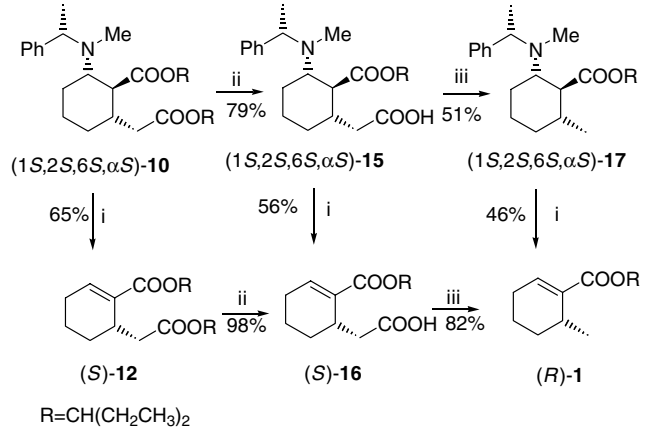
Oxidation of (1*S*,2*S*,6*S*,α*S*)-**10** with *m*-chloroperbenzoic acid (Scheme 4) generated the expected cyclohexene derivative (*S*)-**12**, $[\alpha]_D^{20} = +11.5$ (*c* 0.6, $CHCl_3$), together with the hydroxylamines (1*S*,2*S*,6*S*)-**13** and (*S*)-**14**, in 65%, 17% and 75% yields, respectively. The hydroxylamine **14** derives from the expected Cope elimination of the *trans*-β amino ester moiety within (1*S*,2*S*,6*S*,α*S*)-**10** whereas



Scheme 4. Reagents and conditions: (i) (*S*)-(*N*-methyl-*N*-α-methylbenzylamide [(*S*)-**9**, 1.8 equiv, THF, −78 °C]; (ii) (*S*)-(*N*-methyl-*N*-α-methylbenzylamide [(*S*)-**9**, 1.2 equiv, THF, −78 °C]; (iii) *m*-CPBA (2.2 equiv), 18 h.

hydroxylamine (1*S*,2*S*,6*S*)-**13** derives from elimination in the α-methylbenzyl moiety.

Selective ester hydrolysis of (*S*)-**12** and (1*S*,2*S*,6*S*,α*S*)-**10** with $LiOH{\cdot}H_2O$ in $MeOH/THF/H_2O$ afforded, respectively (*S*)-**16** and (1*S*,2*S*,6*S*,α*S*)-**15**[8] in quantitative and 79% yields, respectively (Scheme 5). To generate a methyl group attached to the cyclohexane ring, both compounds were subjected to Barton's thiohydroxamic ester radical decarboxylation protocol,[13,14] providing efficiently in the first case, (*R*)-**1** with 82% isolated yield after flash chromatography, $[\alpha]_D^{20} = +46.0$ (*c* 0.5, $CHCl_3$), and (1*S*,2*S*,6*R*)-**17**, in the second $[\alpha]_D^{20} = -6.2$ (*c* 0.7, $CHCl_3$), in 51% isolated yield. Similarly, when (1*S*,2*S*,6*R*)-**17** was subjected to the Cope elimination protocol described before, (*R*)-**1** was



Scheme 5. Reagents and conditions: (i) *m*-CPBA (2.2 equiv); (ii) $LiOH{\cdot}H_2O$, $MeOH/THF/H_2O$ 3:1:1; (iii) 2,2′-dithiopyridine-1,1′-di-*N*-oxide, PPh_3, ^tBuSH, *hv*.

obtained in 46% isolated yield after column chromatography, together with the related cyclohexanyl hydroxylamine in 33% yield. The highest yielding (42% overall) route to the final product is **4d** → (1*S*,2*S*,6*S*,α*S*)-**10** → (*S*)-**12** → (*R*)-**1**, $\eta_{global} = 42\%$.

Neither Cope elimination, ester hydrolysis or Barton decarboxylation involve the C-6 configuration that therefore remains as generated in the first addition–cyclisation reaction. In confirmation ^1H NMR in the presence of the chiral shift reagent (9-anthryl-trifluoroethanol) does not show the splitting of the methyl group signal, which is clearly observed when the racemic compound ethyl (±)-6-methyl-cyclohex-3-enecarboxylate (±)-**1b**,[15] was analysed similarly (2:1 chiral shift reagent:substrate), and an ee >95% can therefore be assigned for (*R*)-**1**. Importantly, the analogous series of reactions deploying the enantiomeric lithium amide (*R*)-**9**, in the initial conjugate addition step will obviously allow simple access to (*S*)-**1**.

3. Conclusion

In conclusion, an expeditious synthesis of pent-3-yl (*R*)-6-methyl-cyclohex-1-ene carboxylate (*R*)-**1** in only four steps from dipent-3-yl (*E*,*E*)-nona-2,7-diendioate **4** as the prochiral precursor and in 42% overall yield was achieved. The highly stereoselective domino reaction initiated by the Michael addition of chiral (*S*)-**9** provide the required (*R*)-configuration in the final product. With the cyclohexane adduct (1*S*,2*S*,6*S*,α*S*)-**10** in hand, the sequence: Cope elimination, selective hydrolysis of the less steric demanding ester and efficient Barton decarboxylation generates the C-6 methyl group without loss of the stereochemical integrity.

The described product can be considered a precursor of pumiliotoxin-(C), and further investigation to this end is underway.

Acknowledgements

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8. All new compounds were fully characterised including elemental analysis or high resolution mass spectrometry. ^{1}H NMR (400 MHz) spectroscopy including two-dimensional homonuclear COSY, heteronuclear HMQC and HMBC, NOE and ROESY experiments for (1*R*,2*R*,6*R*)-**6** and (1*S*,2*S*,6*S*,α*S*)-**15** are in accordance with the structure and stereochemistry assigned.
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10. To the best of our knowledge, this is the first example in which this chiral auxiliary is debenzylated to produce the nitro oxidation state.
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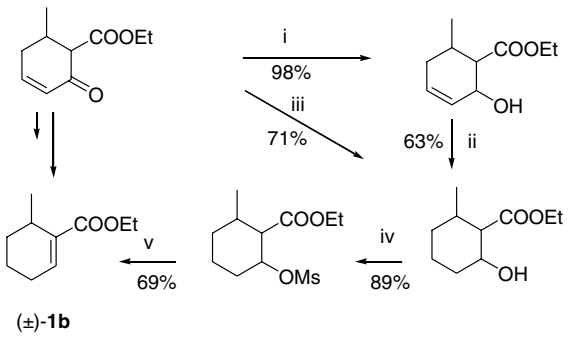
15. The synthesis of (±)-**1b** was achieved in 44% overall yield in four steps, starting from commercially available ethyl 6-methyl-2-oxocyclohex-3-enecarboxylate as follows:



(±)-**1b**

Reagents and conditions: (i) $NaBH_4/CeCl_3/MeOH$; (ii) H_2/Pd–C/EtOAc; (iii) $NaBH_4$/Pyr; (iv) $MsCl/Et_3N$/DCM; (v) DBU/THF/Δ.