An Efficient Asymmetric Synthesis of Cascarillic Acid

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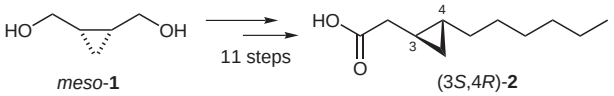
Abstract: An efficient six-step asymmetric synthesis of the cyclopropane containing natural product cascarillic acid in 41% overall yield is described. The key synthetic steps involve the use of a temporary stereogenic hydroxyl group to control the facial selectivity of a directed cyclopropanation reaction and its subsequent removal via a retro-aldol reaction.

Key words: cascarillic acid, cyclopropane, aldol, retro-aldol, temporary stereocentre

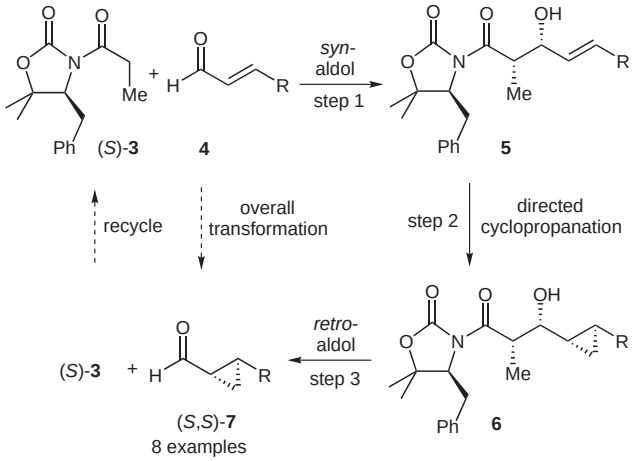
Cascarillic acid [(3*S*,4*R*)-**2**] is a major component of cascarilla essential oil that has been used for many years in the treatment of colds and bronchitis.[1] It contains a *trans*-cyclopropane ring within its fatty acid chain, which contrasts with the majority of naturally occurring cyclopropane fatty acids that are *cis* in orientation.[2] Baird and co-workers have recently confirmed the absolute stereochemistry of this natural product to be 3*S*,4*R* through its total synthesis in 11 steps from *meso*-*cis*-1,2-dihydroxymethylcyclopropane (**1**, Scheme 1).[3] This synthesis included an enzymatic desymmetrisation step to introduce the stereogenic centres of the cyclopropane ring, and an epimerisation step to invert a *cis*-cyclopropane ring into its corresponding *trans*-isomer. Consequently, we now report on an alternative synthetic strategy that affords cascarillic acid **2** in six steps from the chiral auxiliary (*R*)-*N*-isovaleroyl-4-benzyl-5,5-dimethyl-oxazolidin-2-one (**11**).



meso-**1** (3*S*,4*R*)-**2**

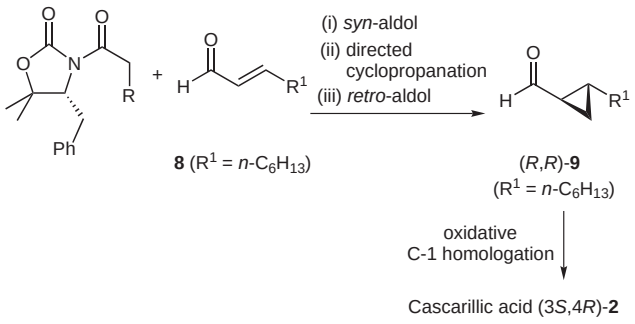
Scheme 1 A previous asymmetric synthesis of cascarillic acid (**2**).

We have recently reported the development of novel synthetic strategies to reversibly generate temporary stereogenic centres that may be used to create remote stereocentres using substrate directable reactions.[4–6] In one of these reports, a novel three-step aldol–directed cyclopropanation–retro-aldol protocol was demonstrated for the asymmetric synthesis of chiral cyclopropane carboxaldehydes in high ee (Scheme 2).[4] In this approach, chiral auxiliary fragment **3** reacts with an α,β-unsaturated aldehyde **4** to give *syn*-aldol product **5** (step 1), whose 'temporary' β-hydroxyl functionality is used to control facial selectivity in a directed cyclopropanation reaction to afford cyclopropane **6** in very high de (step 2). Retro-aldol cleavage of cyclopropane **6** results in destruction of the 'temporary' β-hydroxyl stereocentre, affording the chiral auxiliary fragment **3** and the desired enantiopure cyclopropane carboxaldehyde **7** in very high ee (step 3).



Scheme 2 Three-step *syn*-aldol–cyclopropanation–retro-aldol protocol for the asymmetric synthesis of cyclopropane carboxaldehydes.

We anticipated that this cyclopropanation methodology was ideally suited to the preparation of cascarillic acid (3*S*,4*R*)-**2**, since employing (*E*)-non-2-enal **8** as an aldehyde substrate in this three-step protocol would result in formation of enantiopure cyclopropane carboxaldehyde (*R*,*R*)-**9**. This aldehyde **9** could then be converted to cascarillic acid (3*S*,4*R*)-**2** via an oxidative one-carbon homologation reaction using well established dithiane–Peterson elimination methodology[7,8] (Scheme 3).



Scheme 3 Proposed asymmetric synthesis of cascarillic acid (**2**).

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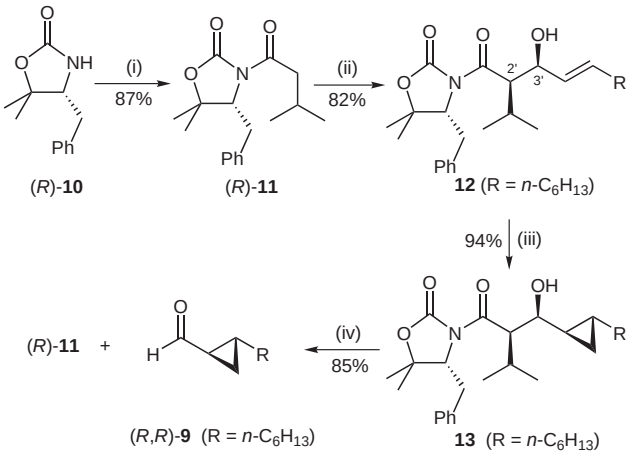
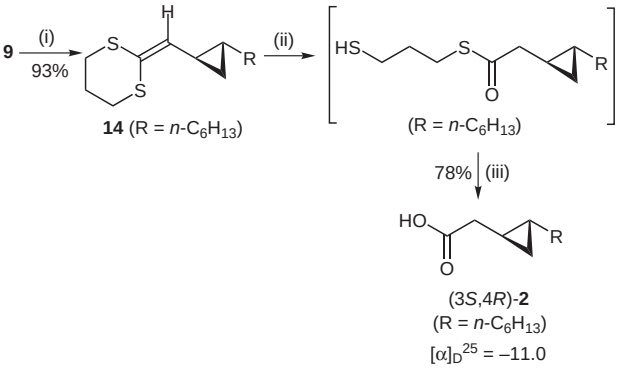
Therefore, our first goal was to employ the *syn*-aldol–directed cyclopropanation–retro-aldol methodology described in Scheme 2 for the asymmetric synthesis of cyclopropane (*R*,*R*)-**9** in high de (Scheme 4). Research within our group investigating steric factors that influence the retro-aldol reaction of α-alkyl-β-hydroxy-*N*-acyl-oxazolidin-2-ones had revealed that *N*-isovaleroyl-oxazolidin-2-one (**11**) was particularly well suited as a chiral auxiliary for this methodology. Therefore, (*R*)-4-benzyl-5,5-dimethyl-oxazolidin-2-one (**10**)[9] was first prepared in 72% yield from unnatural D-phenylalanine using a previously reported procedure.[10] Treatment of 5,5-dimethyl-oxazolidin-2-one [(*R*)-**10**] in THF at –78 °C with 1.1 equivalents of *n*-BuLi, followed by addition of 1.1 equivalents of isovaleroyl chloride gave *N*-isovaleroyl-oxazolidin-2-one [(*R*)-**11**] in 87% yield. Treatment of *N*-acyl-oxazolidin-2-one [(*R*)-**11**] with 1.1 equivalents of 9-BBN-OTf, *i*-Pr_2NEt in CH_2Cl_2 at 0 °C, followed by cooling to –78 °C and addition of (*E*)-non-2-enal (**8**) resulted in *syn*-aldol **12** in 93% de, which was purified to >95% de in 82% yield via silica gel chromatography.[11] The *syn*-stereochemistry of aldol **12** was confirmed from the $J_{(2',3')}$ coupling constant of 6.5 Hz observed in its ^1H NMR spectra.[12] Reaction of *syn*-aldol **12** with 5 equivalents of Et_2Zn and CH_2I_2 in CH_2Cl_2 at 0 °C, resulted in a highly stereoselective cyclopropanation reaction to afford *syn*-cyclopropyl aldol **13** in >95% de and 94% yield.[13] Cyclopropanation under under modified Furukawa conditions are normally *syn*-selective due to minimisation of $A^{1,3}$ strain in the transition state, and as a consequence the absolute configuration of cyclopropane **13** was assigned accordingly.[14] Treatment of cyclopropane **13** with 1.1 equivalents of KHMDS in THF at –40 °C afforded a potassium alkoxide that underwent a clean retro-aldol reaction to give the parent chiral auxiliary (*R*)-**11** and the desired 2-hexyl-cyclopropanecarboxaldehyde (*R*,*R*)-**9** in 85% yield.



Scheme 4 *Reagents and conditions*: (i) *n*-BuLi, isovaleroyl chloride, THF, –78 to 0 °C; (ii) 9-BBN-OTf, *i*-Pr_2NEt, CH_2Cl_2, 0 °C; (*E*)-non-2-enal (**8**), –78 °C to r.t.; (iii) Et_2Zn, CH_2I_2, CH_2Cl_2, –10 °C to 0 °C, 2 h; (iv) KHMDS, THF, –40 °C, 3 h.

With (*R*,*R*)-2-hexylcyclopropanecarbaldehyde (**9**) in hand, treatment with the lithium anion of (1,3-dithian-2-yl)trimethylsilane in THF at –30 °C resulted in nucleophilic addition of the dithiane anion to the aldehyde functionality, followed by subsequent Peterson elimination to afford 2-{[(*R*,*R*)-2-hexylcyclopropyl]methylene}-1,3-dithiane (**14**) in >95% de and 93% yield. Therefore, this reaction was successful in establishing the correct oxidation state of the homologated carbon atom, with no epimerisation of the cyclopropane ring being observed. Treatment of ketene thioacetal **14** under sequential acid and base-catalysed hydrolysis conditions gave cascarillic acid **2** in >95% de and 78% yield, whose spectroscopic data was identical to that previously published for this compound (Scheme 5). The negative sign obtained for the specific rotation of this synthetic sample of cascarillic acid **2** of $[\alpha]_D^{25}$ –11.0 (*c* 0.41, $CHCl_3$); {lit. 1a: $[\alpha]_D^{25}$ –10.5 (*c* 0.553, $CHCl_3$)}, confirmed that we had synthesised the correct enantiomer of this natural product.[3,15]



Scheme 5 *Reagents and conditions*: (i) *n*-BuLi, (1,3-dithian-2-yl)trimethylsilane, THF, 0 °C, 1 h, then (*R*,*R*)-**9**, –30 °C, 2 h; (ii) *p*-TSA, THF–H_2O, 6 h, reflux; (iii) KOH, acetone–H_2O, 2 h, reflux.

In conclusion, we have described an efficient six-step asymmetric synthesis of the cyclopropane containing natural product cascarillic acid in 41% overall yield. The key synthetic steps employed involve the use of a temporary stereogenic hydroxyl group to control the facial selectivity of a directed cyclopropanation reaction, and its subsequent removal via a retro-aldol reaction. The application of this methodology to the asymmetric synthesis of other cyclopropane containing natural products will be reported in due course.

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(*R*)-4-Benzyl-3-[(*E*)-(2*R*,3*S*)-3-hydroxy-2-isopropyl-undec-4-enoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (12): $[\alpha]_D^{25}$ +22.0 (*c* 0.85, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.11 (5 H, m, Ph), 5.54–5.71 (2 H, m, C*H*=CHCH$_2$ and CH=C*H*CH$_2$), 4.53 (1 H, dd, *J* = 10.0, 4.0 Hz, C*H*N), 4.36 (1 H, app. t, *J* = 6.5 Hz, C*H*OH), 4.09 (1 H, dd, *J* = 9.0, 6.5 Hz, COC*H*), 3.09 (1 H, dd, *J* = 14.5, 4.0 Hz, CH_AH$_B$Ph), 2.81 (1 H, dd, *J* = 14.5, 10.0 Hz, CH$_A$*H*$_B$Ph), 2.04–1.88 [4 H, obs. m, O*H*, CH=CHCH_2 and C*H*(CH$_3$)$_2$], 1.35–1.12 [8 H, m, (CH_2)$_4$], 1.24 [6 H, app. s, (CH_3)$_2$C], 0.90 [3 H, d, *J* = 7.0 Hz, CH(CH_3)CH$_3$], 0.82 [3 H, obs. d, *J* = 7.0 Hz, CH(CH$_3$)CH_3], 0.80 (3 H, obs. t, *J* = 7.0 Hz, CH$_2$CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.7, 153.9, 137.4, 135.8, 129.5, 129.1, 128.9, 127.2, 82.4, 73.8, 64.3, 54.1, 35.9, 32.7, 32.1, 29.5, 29.3, 28.7, 28.6, 23.0, 22.6, 21.0, 20.4, 14.5. IR (film): 3501 (br OH), 1778 (C=O$_{ox}$), 1693 (C=O) cm^{-1}. HRMS (ES): *m*/*z* calcd [M + NH$_4$]$^+$: 447.3217; found: 447.3213.
(*R*)-4-Benzyl-3-{(*R*)-2-[(*S*)-[(1*R*,2*R*)-2-hexylcyclopropyl](hydroxy)methyl]-3-methylbutanoyl}-5,5-dimethyl-1,3-oxazolidin-2-one (13): $[\alpha]_D^{25}$ –21.0 (*c* 0.62, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.18 (5 H, m, Ph), 4.56 (1 H, dd, *J* = 10.0, 3.5 Hz, C*H*N), 4.22 (1 H, dd, *J* = 8.5, 6.0 Hz, COC*H*), 3.39 (1 H, dd, *J* = 8.5, 6.0 Hz, C*H*OH), 3.23 (1 H, dd, *J* = 14.5, 3.5 Hz, CH_AH$_B$Ph), 2.86 (1 H, dd, *J* = 14.5, 10.0 Hz, CH$_A$CH_BPh), 2.31 [1 H, m, (CH$_3$)$_2$C*H*], 1.85 (1 H, br s, OH), 1.44–1.20 [10 H m, (CH_2)$_5$], 1.34 [3 H, s, (CH_3)C(CH$_3$)], 1.33 [3 H, s, (CH$_3$)C(CH_3)], 1.02 [3 H, d, *J* = 7.0 Hz, CH(CH_3)CH$_3$], 1.00 (1 H, obs. m, cyc-C*H*), 0.93 [3 H, d, *J* = 7.0 Hz, CH(CH$_3$)CH_3], 0.88 (3 H, t, *J* = 7.0 Hz, CH$_2$CH_3), 0.76 (1 H, m, cyc-C*H*), 0.43 (1 H, app. dt, *J* = 8.5, 4.5 Hz, cyc-CH_AH$_B$), 0.28 (1 H, app. dt, *J* = 8.5, 5.0 Hz, cyc-CH$_A$*H*$_B$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.1, 153.7, 137.5, 129.4, 129.1, 127.2, 82.2, 75.5, 64.4, 54.5, 35.8, 34.2, 32.3, 29.6, 29.5, 28.8, 28.6, 23.1, 22.8, 22.2, 21.4, 21.1, 18.8, 14.5, 9.6. IR (film): 3516 (br OH), 1778 (C=O$_{ox}$), 1693 (C=O) cm^{-1}. HRMS (ES): *m*/*z* calcd [M + NH$_4$]$^+$: 461.3374; found: 461.3370.
(*R*,*R*)-2-Hexylcyclopropanecarbaldehyde (9): $[\alpha]_D^{25}$ –26.0 (*c* 0.35, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.98 (1 H, d, *J* = 5.5 Hz, C*H*O), 1.61 (1 H, m, C$_1$*H*), 1.51–1.20 [11 H, m, C$_2$*H* and (CH_2)$_5$], 0.96–0.83 (5 H, m, cyc-CH_2 and CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.2, 32.6, 31.7, 30.6, 29.0, 28.9, 22.7, 22.6, 14.9, 14.1. IR (film): 1713 (C=O) cm^{-1}. HRMS (ES): *m*/*z* calcd [M + NH$_4$]$^+$: 172.1696; found: 172.1696.
2-{[(*R*,*R*)-2-Hexylcyclopropyl]methylene}-1,3-dithiane (14): $[\alpha]_D^{25}$ –20.0 (*c* 0.30, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.42 (1 H, d, *J* = 10.0 Hz, C=C*H*), 2.91 (4 H, m, 2 × SCH_2), 2.22–2.13 (2 H, m, SCH$_2$CH_2), 1.58 (1 H, m, C=CHC*H*), 1.41–1.20 [10 H, m, (CH_2)$_5$], 0.88 (3 H, t, *J* = 7.0 Hz, CH$_2$CH_3), 0.79 (1 H, m, cyc-C*H*), 0.65–0.56 (2 H, m, cyc-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.4, 121.6, 34.1, 32.3, 31.3, 30.5, 29.7, 29.5, 26.0, 23.1, 22.2, 20.3, 15.2, 14.5. IR (film):1678 (C=C) cm^{-1}. HRMS (ES): *m*/*z* calcd [M + H]$^+$: 257.1392; found: 257.1393.
2-[(1*S*,2*R*)-2-Hexylcyclopropyl]acetic acid [(3*S*,4*R*)-cascarillic acid] (2): $[\alpha]_D^{25}$ –11.0 (*c* 0.41, $CHCl_3$); lit. 1a: $[\alpha]_D^{25}$ –10.5 (*c* 0.553, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.26 (2 H, app. d, *J* = 7.0 Hz, CH_2CO$_2$H), 1.41–1.18 [10 H, m, (CH_2)$_5$], 0.88 (3 H, t, *J* = 7.0 Hz, CH$_2$CH_3), 0.77 (1 H, m, C$_1$*H*), 0.56 (1 H, m, C$_2$*H*), 0.33 (2 H, m, cyc-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.6, 37.5, 32.8, 30.9, 28.3, 28.1, 21.6, 17.7, 13.1, 13.0, 10.6. IR (film): 1711 (C=O) cm^{-1}. HRMS (EI): *m*/*z* calcd [M]$^+$: 184.1458; found: 184.1458.