Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 6987

www.rsc.org/obc

PAPER

Enantio- and diastereocontrolled conversion of chiral epoxides to *trans*-cyclopropane carboxylates: application to the synthesis of cascarillic acid, grenadamide and L-(−)-CCG-II†

Pradeep Kumar,* Abhishek Dubey and Anand Harbindu

Received 26th March 2012, Accepted 3rd July 2012
DOI: 10.1039/c2ob25622c

An efficient high yielding improved method for the enantio- and diastereoselective cyclopropanation of chiral epoxides using triethylphosphonoacetate and base (Wadsworth–Emmons cyclopropanation) is reported. The utility of this protocol is illustrated by concise and practical synthesis of cascarillic acid, grenadamide and L-(−)-CCG-II, a cyclopropane containing natural products.

Introduction

Cyclopropane ring systems are quite ubiquitous in nature and they constitute the important structural framework of a large number of natural products, medicinally active compounds, drugs, agrochemicals, foods and fragrances (Fig. 1).[1] They also serve as important synthetic intermediates in cyclopentannulation by a reaction involving metal-catalyzed ring-opening of cyclopropanes.[2] Therefore methods to access cyclopropanes in a stereocontrolled manner is of paramount importance. A great deal of effort has been put by synthetic organic chemists worldwide into the development of stereoselective methods for cyclopropanes.[3] Some of the commonly employed methods include the metal-mediated carbene insertion into alkenes,[4] asymmetric variants of the Simmons–Smith reaction,[5] Corey–Chaykovsky reactions,[6] Kulinkovich–de Meijere reactions,[7] and Michael-initiated ring closure reactions.[8] Besides in recent years there has been a considerable upsurge of interest in developing enantioselective methods for cyclopropanation that are based on organocatalysis.[9] Despite these advances, on a commercial scale, the wasteful enzymatic resolution still remains the method of choice for all practical purposes.[10]

Way back in 1961, Wadsworth and Emmons developed a method for the direct conversion of epoxides to cyclopropyl esters.[11] This reaction is known to provide straightforward access to a variety of cyclopropanes from readily available enantiopure epoxides and phosphonate.[12] Very recently Bray *et al.* have explored and extended the scope of this method to the stereocontrolled synthesis of quaternary cyclopropyl esters[13a] and *trans*-cyclopropyl sulfones from terminal epoxides.[13b]

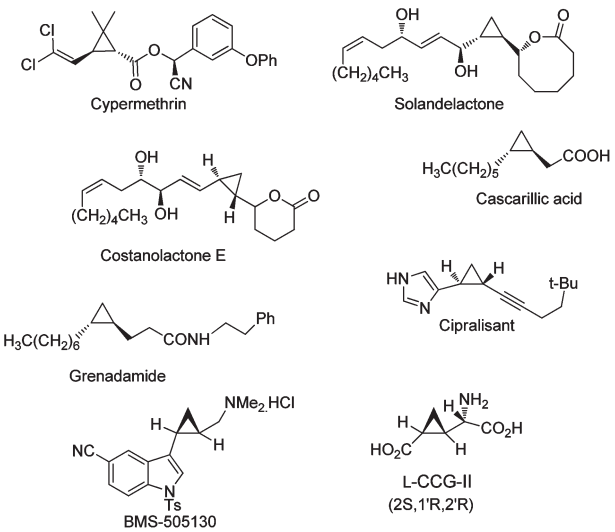
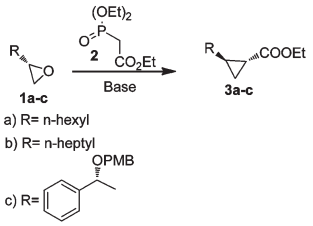


Fig. 1 Structures of some important cyclopropane containing molecules.

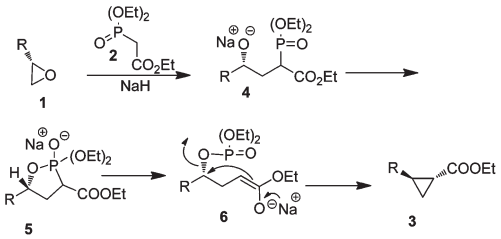
In some of the earlier reports, it was shown that the transformation of epoxide to cyclopropane proceeds in an S_N2 fashion with some degree of inversion at the epoxide stereocentre.[12k,l] This crucial observation was further revisited by Armstrong and Scutt[12d] who demonstrated that (*R*)-styrene oxide/(*S*)-glycidol benzyl ether can be converted into the corresponding cyclopropane derivatives with complete inversion of configuration in >95% ee albeit in 51% and 63% yields respectively. Subsequently, the scalability of this process was demonstrated by researchers from Bristol-Myers-Squibb and Eli Lilly pharmaceutical research institute for substituted styrene derived epoxides in appreciable yields and with excellent enantioselectivity.[12a,e] The previous literature reports known to produce the cyclopropyl esters lack substrate generality and also

Division of Organic Chemistry, National Chemical Laboratory, Pune 411008, India. E-mail: pk.tripathi@ncl.res.in; Tel: +91-20-25902050; Fax: +91-20-25902629

†Electronic supplementary information (ESI) available: ^{1}H NMR, ^{13}C NMR spectra of compounds **3a**, **7**, **8**, **9**, **3b**, **10**, **11**, **13**, **17**, **18**, **19**, **15**, **1c**, **3c**, **20**, **15**, **21**, **14**, experimental procedures of compounds **7**, **3b**, **12**, **18**, **19**, **15**. See DOI: 10.1039/c2ob25622c



Scheme 1 Diastereocontrolled synthesis of cyclopropyl esters (**3a–c**).



Scheme 2 Mechanistic pathway for the transformation of epoxides to cyclopropane carboxylates.

suffer either from poor diastereoselectivity or low yields (20–60%).[11,12f,k,m,n] Therefore it was considered worthwhile to develop a general, high yielding stereo- and enantiocontrolled method for cyclopropanation, with a view to its application for the total synthesis of biologically active natural products. Herein we report our successful endeavors towards stereoselective conversion of epoxide to *trans*-selective cyclopropyl esters and its application to the total synthesis of cascarillic acid, grenadamide and L-(−)-CCG-II.

Results and discussion

As illustrated in Scheme 1, the enantiopure epoxides (**1a–c**) were treated with triethylphosphonoacetate (TEPA) **2** in the presence of a base to give the *trans*-selective cyclopropyl esters (**3a–c**). In order to examine efficiency and generality of this method, the reaction with three different substrates (**1a–c**) was studied using triethyl phosphonoacetate and NaH as a base. The required *trans*-selective[14] cyclopropane carboxylates (**3a–c**) were obtained in excellent yield and good enantiomeric excess.[15] The reaction mechanism for the formation of *trans*-selective cyclopropyl ester involves ring opening of epoxide **1** with the anion of phosphonate **2** to give **4** which eventually leads to the cyclic phosphonate **5**. The intermediacy of such an intermediate has been first proposed by Wadsworth and Emmons for the cyclopropanation reaction.[11] Subsequent migration of diethyl phosphate from C to O in the cyclic phosphonate intermediate **5** produces **6** which undergoes stereospecific S_N2 intramolecular ring closure furnishing the corresponding cyclopropyl derivative **3** with complete inversion of configuration at the epoxide centre (Scheme 2). A clean stereochemical inversion of an aryl epoxide has been also reported by two groups independently.[12d,e]

As a part of our research interest aimed at developing new methodologies[16a,b] and their application towards the synthesis of natural products,[16c–h] we considered developing optimised reaction conditions for stereocontrolled high yielding synthesis of cyclopropyl esters. Towards this end, we have chosen commercially available (*S*)-2-hexyloxirane **1a** for our study. It is important to note that in the Wadsworth–Emmons cyclopropanation reaction, a better solubility of the TEPA anion in organic solvent is very important for the efficacy of the reaction. Among the various solvents screened, toluene and DME (dimethoxyethane) were found to be the most suitable solvent for this reaction. A careful monitoring of the reaction revealed that at 80 °C, most of the epoxide was consumed in *ca.* 12 h, however, the reaction mixture contained about 5–10% of intermediates. Once the epoxide was consumed, the reaction temperature could be raised to 110 °C to burn off the remaining intermediates. Additionally while 2 equiv. of phosphonate gave only a 60% yield of **3a**, a substantial improvement in the yield (85%) was observed with 4 equiv. of phosphonate. Thus under the optimised conditions higher optical (95% ee) and chemical yields (85%) of cyclopropyl ester **3a** could be obtained using 4 equiv. of phosphonate and NaH under reflux toluene. Similar results under identical reaction conditions provided the required cyclopropyl ester **3b** in 85% yield and >99% ee from the corresponding chiral epoxide **1b**. Likewise, **1c** furnished **3c** in 75% yield and >99% ee as a single diastereomer.

Having optimised the reaction conditions for Wadsworth–Emmons cyclopropanation, we then turned our attention towards application of this strategy for the synthesis of cyclopropane containing natural products. Herein we wish to report our successful endeavours towards the enantioselective synthesis of cascarillic acid, grenadamide and L-(−)-CCG-II.

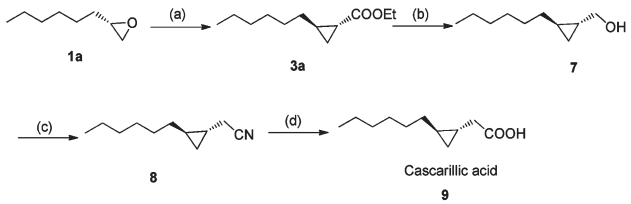
Synthesis of cascarillic acid

Cascarillic acid is a cyclopropane containing fatty acid found in cascarilla essential oil, derived from the bark of the medicinal shrub Croton *eluteria* L.[17a] The oil has been used for many years to treat the symptoms of cold and influenza as well as respiratory ailments including bronchitis, *via* its use as an inhalant. Some methods reported for the synthesis of the target molecule suffer either from multisteps, epimerization steps and unwanted protection and deprotection steps of chiral auxiliary.[17] Taking into account the drawback of reported methods, we considered developing a practical, concise and high-yielding synthesis of the target molecule employing the Wadsworth–Emmons cyclopropanation reaction.

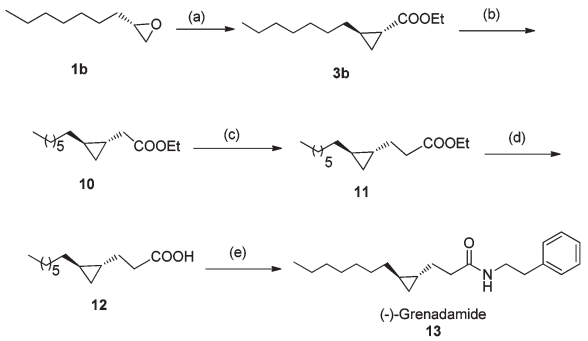
The synthetic sequence for the synthesis of cascarillic acid is shown in Scheme 3. Commercially available (*S*)-2-hexyloxirane **1a** was subjected to optimized Wadsworth–Emmons cyclopropanation to furnish the ester **3a** in excellent yield. The ester group was subjected to reduction with $LiAlH_4$ to furnish alcohol **7** in 80% yield, which was converted into nitrile **8** using a combination of Me_3SiCl–NaCN (1 : 1) and a catalytic amount of NaI in excellent yield. Finally nitrile **8** was converted into acid **9** by basic hydrolysis in 75% yield. We thus accomplished the synthesis of cascarillic acid in four steps and 41% overall yield. The physical and spectroscopic data of **9** were in full agreement with those reported in the literature.[17b]

Synthesis of (−)-grenadamide

Grenadamide **13** was isolated from the marine cyanobacterium *Lyngbya majuscula* by Sitachitta and Gerwick in 1998.[18] The



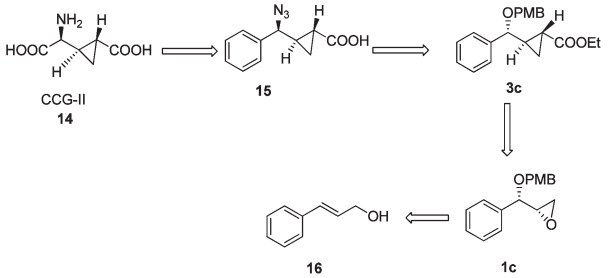
Scheme 3 *Reagents and conditions*: (a) $(EtO)_2POCH_2COOEt$, NaH, toluene, 80 °C (8 h) then 110 °C (6 h), 85%; (b) $LiAlH_4$, THF, −10 °C, 80%; (c) Me_3SiCl, NaCN (1 : 1), NaI (cat), DMF–acetonitrile, 65 °C, 80%; (d) 3 N NaOH, MeOH, reflux, 75%.



Scheme 4 *Reagents and conditions*: (a) $(EtO)_2POCH_2COOEt$, NaH, toluene, 80 °C (8 h) then 110 °C (6 h), 85%; (b) $LiCHBr_2$–(*n*-BuLi–tetramethyl piperidine–dibromomethane), −90 °C then *n*-BuLi, −90 °C to rt, acidic EtOH, 55%; (c) $LiCHBr_2$–(*n*-BuLi–tetramethyl piperidine–dibromomethane), −90 °C then *n*-BuLi, −90 °C to rt, acidic EtOH, 60%; (d) LiOH, MeOH–H_2O (3 : 2), 82%; (e) $SOCl_2$, $PhCH_2CH_2NH_2$, 4 h, 65%.

structurally unique cyclopropyl fatty acid derived metabolites were shown to demonstrate cannabinoid receptor binding activity, as well as cytotoxicity towards cancer cells. Few syntheses[19] of this molecule have been described, to overcome some of the drawbacks associated with the reported methods we considered developing a facile and expeditious synthesis of the target molecule **13**.

The synthesis of (−)-grenadamide started from commercially available epoxide **1b** as illustrated in Scheme 4. The epoxide **1b** was converted into the cyclopropyl ester **3b** in 85% yield and >99% ee.[15] The optical purity and stereochemistry was determined by comparison of the sign of rotation with the literature values.[19d] In order to prepare compound **11**, we decided to convert ester **3b** into the corresponding aldehyde followed by the 2-C Wittig reaction, but we observed epimerization of the chiral center in aldehyde. We then turned our attention towards sequential homologation of ester. The ester group of compound **3b** was double homologated[20] to furnish compound **11** in moderate yield over two steps by using a combination of $LiCHBr_2$ and *n*-BuLi reagent. The ester hydrolysis under basic conditions using LiOH furnished acid **12** in 82% yield. Conversion of acid into acid chloride by using $SOCl_2$ and subsequent coupling with phenylethylamine furnished grenadamide **13** in 65% yield. The physical and spectroscopic data of **13** were in full agreement with those reported.[19b]



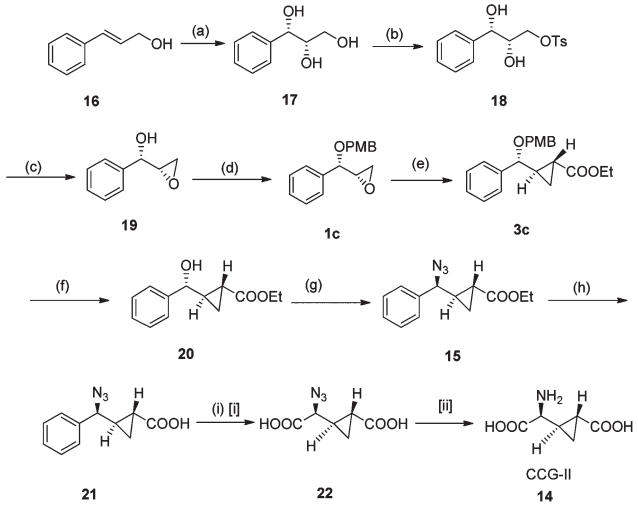
Scheme 5 Retrosynthetic route to L-CCG-II.

Synthesis of L-(−)-CCG-II

As a pharmacological tool, L-CCG-II **14** has played an important role for the investigation of the mechanism underlying the glutamate function as well as the design of useful therapeutic drugs of various neuronal diseases.[21] A great deal of attention has been paid to the modification of these compounds, which has led to the discovery of several other potent and selective agonists or antagonists for mGluRsa. Encouraged by our earlier results we further became interested in extending the scope of optimized Wadsworth–Emmons cyclopropanation for the total synthesis of L-CCG-II **14**.[22] We now wish to report successful application of our strategy for the synthesis of the target compound from commercially available cinnamyl alcohol **16** employing Sharpless asymmetric dihydroxylation (AD)[23] and Wadsworth–Emmons cyclopropanation as the key steps. Our synthetic approach for the synthesis of L-CCG-II was envisioned *via* the retrosynthetic route as shown in Scheme 5. The compound **14** could be obtained from compound **15** by series of reactions involving oxidation of the phenyl ring and reduction of azide into amine. The compound **15** could be derived from **3c** by ester hydrolysis and conversion of alcohol into azide. The compound **3c** could be obtained from epoxide **1c** by the Wadsworth–Emmons cyclopropanation reaction. The epoxide **1c** in turn could be easily synthesized by the Sharpless asymmetric dihydroxylation (AD) of cinnamyl alcohol **16**.

The synthesis of L-CCG-II **14** started from commercially available cinnamyl alcohol **16** as illustrated in Scheme 6. Cinnamyl alcohol **16** was subjected to Sharpless asymmetric dihydroxylation using OsO_4 and $K_3Fe(CN)_6$ as a co-oxidant in the presence of $(DHQ)_2PHAL$ as the ligand to give triol **17** in 84% yield and 95% ee.[24] The regioselective primary monotosylation[25] of triol **17** with tosyl chloride and a catalytic amount of Bu_2SnO furnished the tosyl diol **18** in 89% yield. Base treatment of compound **18** in the presence of K_2CO_3 in methanol furnished epoxy alcohol **19** in 79% yield. The free hydroxy group of **19** was then protected as PMB ether using PMB-bromide to give **1c** in 86% yield. With epoxide **1c** in hand, our next aim was to construct the cyclopropane ring.

Towards this end, we used the optimized Wadsworth–Emmons cyclopropanation reaction to furnish **3c** as a single diastereomer in 75% yield and >99% ee. In order to introduce an amino group, PMB-protected hydroxyl was deprotected by DDQ to furnish the free alcohol **20** in 85% yield. The hydroxyl group of **20** was converted into *O*-mesylate, followed by the nucleophilic displacement with NaN_3 in dry DMF to afford compound **15** in 85% yield. Compound **15** was then subjected to ester



Scheme 6 *Reagents and conditions*: (a) $(DHQ)_2PHAL$ (1 mol%), 0.1 M OsO_4 (0.4 mol%), $CH_3SO_2NH_2$, K_2CO_3, $K_3Fe(CN)_6$, *t*-BuOH–H_2O (1 : 1), 30 h, 84%; (b) TsCl, Et_3N, CH_2Cl_2, Bu_2SnO, 0 °C, 6 h, 89%; (c) K_2CO_3, MeOH, 15 min, 79%; (d) PMBBr, NaH, THF, 0 °C, 6 h, 86%; (e) $(EtO)_2POCH_2COOEt$, NaH, toluene, 80 °C to 110 °C, 14 h, 75%; (f) DDQ, CH_2Cl_2–H_2O (18 : 1), 3 h, 85%; (g) (i) MsCl, Et_3N, DMAP, CH_2Cl_2, 1 h; (ii) NaN_3, DMF, 60 °C, 8 h, 85%; (h) LiOH, MeOH–H_2O (3 : 2), 5 h, 82%; (i) [i] $RuCl_3$, $NaIO_4$, 70 °C, 15 min; [ii] $Pd(OH)_2$, H_2, MeOH, 2 h, for two steps 72%.

hydrolysis by using LiOH to furnish the acid **21** in 82% yield. Compound **21** was subjected to phenyl group oxidation[26] by using a combination of $RuCl_3{\cdot}3H_2O$ and $NaIO_4$ to furnish the diacid **22**, which unfortunately underwent decomposition during work-up and purification. We then decided to directly proceed to the next step of reduction of azide into amine by using $Pd(OH)_2$ without column purification of diacid **22** furnishing L-CCG-II **14** in 72% yield (over two steps). The physical and spectroscopic data were identical with those reported.[22c] The overall yield of the target compound **14** was found to be 16% from nine steps.

Conclusion

In summary, we have developed a facile and practical enantioselective synthesis of cascarillic acid, grenadamide and L-CCG-II. The key step involves an improved high yielding direct transformation of epoxide to enantiopure cyclopropane carboxylate. The synthetic strategy is flexible and would permit maximum variability in product structure with regard to stereochemical diversity which is particularly important for making various synthetic analogues required for the screening of biological activity.

Experimental section

(1*R*,2*R*)-Ethyl 2-hexylcyclopropanecarboxylate (3a)

To a suspension of sodium hydride (4.67 g, 116.97 mmol, 60% in mineral oil) in toluene (100 mL) at 0 °C was added triethylphosphonoacetate (31 mL, 155.99 mmol) dropwise over 30 min. After stirring for 10 min, epoxide **1a** (5 g, 38.99 mmol) in 20 mL of toluene was added dropwise over 20 min, followed by heating at 80 °C for 8 h, then raising the temperature up to 110 °C. After completion of the reaction (6 h), the solution was cooled to room temperature, diluted with EtOAc (100 mL), then washed with saturated aqueous NH_4Cl (100 mL). After drying over Na_2SO_4 and concentration *in vacuo*, the crude material was purified by flash chromatography using petroleum ether–EtOAc (98 : 2) as the eluent, to give the desired cyclopropane derivative **3a** (6.57 g, 85% yield) as a syrupy colorless oil. $[\alpha]_D^{25}$ −58.8 (*c* 1.2, $CHCl_3$); {lit.:[19d] $[\alpha]_D^{20}$ +61.9 (*c* 1.17, $CHCl_3$) for **ent-3a**}; IR (neat, cm^{-1}): ν_{max} 2927, 2958, 2856, 1727, 1613, 1583, 1452, 1410, 1177, 1097, 757; ^1H NMR (400 MHz, $CDCl_3$): δ 0.63–0.72 (1H, m), 0.88 (3H, t, *J* 5.2 Hz), 1.04–1.34 (16H, m), 4.1 (2H, q, *J* 7.0, 14.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 14.2, 15.4, 20.1, 22.5, 22.8, 28.9, 29.0, 31.7, 33.0, 60.2, 174.5; MS(ESI): *m*/*z* 221.30 $(M + Na)^+$.

2-((1*S*,2*R*)-2-Hexylcyclopropyl)acetonitrile (8)

A solution of the alcohol **7** (2.0 g, 12.10 mmol), NaCN (1.25 g, 25.59 mmol), NaI (5–10 mg) in CH_3CN (20 mL) and DMF (10 mL) was deaerated, under an argon atmosphere, and Me_3SiC1 (3.24 mL, 25.29 mmol) was added at room temperature. The mixture was then placed in a preheated (60–65 °C) oil bath and heated with stirring for 6 h. After consumption of the starting material, the mixture was poured into H_2O (100 mL) and the mixture extracted with Et_2O (100 mL). The organic phase was washed with H_2O (5 × 50 mL) and with brine (50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Silica gel column chromatography of the crude product using petroleum ether–EtOAc (95 : 5) as the eluent gave **8** (1.69 g, 80% yield) as a pale yellow color syrupy liquid; $[\alpha]_D^{25}$ −17.9 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 2927, 2251, 1460, 1215, 668; ^1H NMR (200 MHz, $CDCl_3$): δ 0.37–0.51 (2H, m), 0.60–0.81 (2H, m), 0.89 (3H, t, *J* 6.6 Hz), 1.15–1.5 (10H, m), 2.36 (2H, dd, *J* 2.3, 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.9, 13.9, 14.0, 18.9, 21.5, 22.5, 29.0, 29.2, 31.7, 33.3, 118.8; MS (ESI): *m*/*z* 188.16 $(M + Na)^+$. Elemental analysis (%) calcd for ($C_{11}H_{19}N$): C, 79.94; H, 11.59; N, 8.47%; Found: C, 79.75; H, 11.70; N, 8.23%.

2-((1*S*,2*R*)-2-Hexylcyclopropyl)acetic acid (9)

A solution of nitrile **8** (1.0 g, 6.05 mmol) and 20 mL of 3 N NaOH in 58 mL of methanol was refluxed for 6 h. Then the reaction mixture was cooled to 0 °C, acidified to pH 5 with 1 M aqueous hydrochloric acid, and partitioned between EtOAc and brine. The organic phase was washed with H_2O (1 × 50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Silica gel column chromatography of the crude product using petroleum ether–EtOAc (8 : 2) as the eluent gave **9** (0.84 g, 75% yield) as a pale yellow color syrupy liquid. $[\alpha]_D^{25}$ −9.8 (*c* 0.50, $CHCl_3$); {lit.:[17b] $[\alpha]_D^{25}$ −10.5 (*c* 0.553, $CHCl_3$)}; IR (neat, cm^{-1}): ν_{max} 3420, 2855, 1711, 1458, 1216, 759, 668; ^1H NMR (400 MHz, $CDCl_3$): δ 0.30–0.37 (2H, m), 0.48–0.64 (1H, m), 0.70–0.91 (4H, m), 1.11–1.47 (10H, m), 2.26 (2H, d, *J* 7.2 Hz), 9.61 (1H, brs); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.0, 13.9, 14.1,

18.9, 22.6, 29.1, 29.3, 32.0, 33.8, 38.9, 179.9; MS (ESI): *m*/*z* 207.31 $(M + Na)^+$.

Ethyl-2-((1*S*,2*R*)-2-heptylcyclopropyl)acetate (10)

To an ice cooled solution of 2,2,6,6-tetramethylpiperidine (5.76 g, 33.9 mmol) in 40 mL of THF, *n*-butyllithium (19.4 mL, 1.6 M in hexane, 31.08 mmol) was added dropwise. This mixture was added dropwise to a stirred solution of dibromomethane (2.17 mL, 31.06 mmol) in 40 mL of THF, cooled with a −90 °C bath (dry ice–diethyl ether). After 5 min, a solution of ethyl ester **3b** (3 g, 14.12 mmol) in 30 mL of THF was added dropwise over 15 min, and 10 min later a solution of *n*-butyllithium (44.15 mL, 1.6 M in hexane, 70.64 mmol) was added dropwise. The −90 °C cooling bath was replaced with a 30 °C water bath, and then stirred for 15 min. The reaction mixture was added *via* a cannula to a rapidly stirred, ice-cooled solution of acidic ethanol (prepared from 5 mL of acetyl chloride in 25 mL of absolute ethanol). The mixture was diluted with 200 mL of ether, washed with 10% sulfuric acid, 5% aqueous sodium bicarbonate, and saturated brine, dried over Na_2SO_4 and concentrated under reduced pressure to give a crude product which was purified by chromatography on silica eluting with petroleum ether–EtOAc (98 : 2) to give homologated ester **10** (1.75 g, 55% yield) as a pale yellow liquid. $[\alpha]_D^{25}$ −13.99 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 2933, 2874, 1736; ^1H NMR (500 MHz, $CDCl_3$): δ 0.29–0.31 (2H, m), 0.47–0.54 (1H, m), 0.75–0.82 (1H, m), 0.88 (3H, t, *J* 6.1 Hz), 1.19–1.35 (15H, m), 2.15–2.25 (2H, m), 4.13 (2H, q, *J* 7.1, 14.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.6, 14.1, 14.2, 14.3, 18.6, 22.7, 29.4, 29.6, 31.9, 33.9, 39.2, 60.2, 173.3. Elemental analysis (%) calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58%; Found: C, 74.33; H, 11.49%.

Ethyl 3-((1*R*,2*R*)-2-heptylcyclopropyl)propanoate (11)

To an ice cooled solution of 2,2,6,6-tetramethylpiperidine (2.7 g, 15.88 mmol) in 40 mL of THF, *n*-butyllithium (9.1 mL, 1.6 M in hexane, 14.56 mmol) was added dropwise. This mixture was added dropwise to a stirred solution of dibromomethane (1 mL, 14.56 mmol) in 40 mL of THF, cooled with a −90 °C bath (dry ice–diethyl ether). After 5 min, a solution of ethyl ester **10** (1.5 g, 6.62 mmol) in 30 mL of THF was added dropwise over 15 min, and 10 min later a solution of *n*-butyllithium (20.7 mL, 1.6 M in hexane, 33.1 mmol) was added dropwise. The −90 °C cooling bath was replaced with a 30 °C water bath, and then stirred for 15 min. The reaction mixture was added *via* a cannula to a rapidly stirred, ice-cooled solution of acidic ethanol (prepared from 5 mL of acetyl chloride in 25 mL of absolute ethanol). The mixture was diluted with 200 mL of ether, washed with 10% sulfuric acid, 5% aqueous sodium bicarbonate, and saturated brine, dried over Na_2SO_4 and concentrated under reduced pressure to give a crude product which was purified by silica gel column chromatography with petroleum ether–EtOAc (96 : 4) to give homologated ester **11** (955 mg, 60% yield) as a colorless syrupy liquid. $[\alpha]_D^{25}$ −13.00 (*c* 1, $CHCl_3$); {lit.:[19a] $[\alpha]_D^{25}$ +12.5 (*c* 0.69, $CHCl_3$) for **ent-11**}; IR (neat, cm^{-1}): ν_{max} 2938, 2871, 1734; ^1H NMR (400 MHz, $CDCl_3$): δ 0.26–0.28 (2H, m), 0.49–0.53 (1H, m), 0.71–0.85 (1H, m), 0.85 (3H, t, *J* 6.3 Hz), 1.22–1.49 (15H, m), 1.56–1.66 (2H, m), 2.28 (2H, t, *J* 7.3 Hz), 4.13 (2H, q, *J* 7.0, 14.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7, 14.1, 14.2, 18.1, 18.8, 22.7, 26.9, 29.3, 29.6, 29.9, 31.9, 32.5, 34.7, 60.1, 173.9; MS (ESI): *m*/*z* 241.33 $(M + H)^+$.

3-((1*R*,2*R*)-2-Heptylcyclopropyl)-*N*-phenethylpropanamide (13)

3-((1*R*,2*R*)-2-Heptylcycloprop-1-yl)propionic acid **12** (100 mg, 0.47 mmol) was treated with thionyl chloride (3 mL) and refluxed for 2 h. The excess of thionyl chloride was distilled off to give a residue of 3-((1*R*,2*R*)-2-heptylcyclopropyl)propionyl chloride. The residue was cooled to 5 °C and treated with phenylethyl amine (0.285 g, 2.35 mmol) under a nitrogen atmosphere. A white precipitate was formed and the reaction was stirred for 2 h. The mixture was diluted with H_2O and the product was extracted with ether (2 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give a crude product which was purified by chromatography on silica eluting with petroleum ether–EtOAc (1 : 1) to give 3-((1*R*,2*R*)-2-heptylcyclopropyl)-*N*-phenethylpropionamide **13** (96 mg, 65% yield) as a pale yellow solid. M.p. 48–49 °C lit.:[19b] 46–47 °C; $[\alpha]_D^{25}$ −11.8 (*c* 1.0, $CHCl_3$); {lit.:[19b] $[\alpha]_D^{25}$ −11.0 (*c* 1.0, $CHCl_3$)}; IR (neat, cm^{-1}): ν_{max} 3320, 2935, 1678, 1560, 1216, 759; ^1H NMR (400 MHz, $CDCl_3$): δ 0.28–0.32 (2H, m), 0.51–0.54 (1H, m), 0.75–0.79 (1H, m), 0.86 (3H, t, *J* 6.7 Hz), 1.09–1.12 (2H, m), 1.13–1.48 (10H, m), 1.54–1.62 (2H, m), 2.12 (2H, t, *J* 7.3 Hz), 2.83 (2H, t, *J* 7.0 Hz), 3.53 (2H, q, *J* 6.7, 13.0 Hz), 5.43 (1H, brs), 7.19–7.43 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.4, 14.1, 18.2, 19.5, 22.6, 27.0, 29.3, 29.6, 29.9, 31.9, 32.6, 35.7, 36.9, 40.5, 126.5, 128.7, 138.9, 173.1; MS (ESI): *m*/*z* 338.49 $(M + Na)^+$.

(1*S*,2*S*)-1-Phenylpropane-1,2,3-triol (17)

To a mixture of $K_3Fe(CN)_6$ (73.61 g, 223 mmol), K_2CO_3 (30.9 g, 223 mmol) and $(DHQ)_2PHAL$ (580.55 mg, 1 mol%) in *t*-BuOH–H_2O (1 : 1, 745.36 mL, 5 mL $mmol^{-1}$) cooled at 0 °C was added OsO_4 (2.98 mL, 0.1 M sol in toluene, 0.4 mol %) followed by methane sulfonamide (7.08 g, 74 mmol). After stirring for 5 min at 0 °C, the olefin **16** (10 g, 74 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 30 h and then quenched with solid sodium sulfite (10 g). The stirring was continued for 45 min and the solution was extracted with EtOAc (5 × 200 mL). The combined organic phases were washed (10% KOH, then brine), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether–EtOAc (3 : 7) as the eluent gave the triol **17** (10.52 g, 85% yield) as a thick syrupy liquid. $[\alpha]_D^{25}$ +20.8 (*c* 3.5, $CHCl_3$); {lit.:[24] $[\alpha]_D^{25}$ +20.92 (*c* 3.68, $CHCl_3$)}; IR (neat, cm^{-1}): 3369, 2932, 1447, 1215, 1008, 770, 702, 668; ^1H NMR (400 MHz, $CDCl_3$): δ 3.26–3.36 (2H, m), 3.64–3.69 (1H, m), 4.3 (3H, brs), 4.54 (1H, d, *J* 7.1 Hz), 7.23–7.27 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 63.0, 74.6, 76.0, 126.7, 127.9, 128.4, 140.5; MS (EI) *m*/*z* (%): 191 $(M + Na)^+$.

(*S*)-2-((*S*)-(4-Methoxybenzyloxy)(phenyl)methyl)oxirane (1c)

To a solution of epoxy alcohol **19** (2.03 g, 13.51 mmol) in dry THF (20 mL) was added sodium hydride (60%, 0.810 g, 20.57 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 °C. To this was added slowly *p*-methoxybenzyl bromide (1.84 mL, 14.86 mmol) and tetra *n*-butylammonium iodide (0.50 g, 1.35 mmol) with further stirring for 6 h at room temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with water (3 × 100 mL), brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether–EtOAc (93 : 7) as the eluent furnished the PMB protected epoxide **1c** (3.14 g, 86% yield) as a colorless oil. $[\alpha]_D^{25}$ +41.3 (*c* 1.8, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3031, 2836, 1612, 1513, 1454, 1248, 1173, 1086, 1035, 821, 754; ^1H NMR (400 MHz, $CDCl_3$): δ 2.60 (1H, dd, *J* 2.6, 4.8 Hz), 2.72–2.77 (1H, m), 3.23–3.29 (1H, m), 3.82 (3H, m), 4.10 (1H, d, *J* = 6.5 Hz), 4.43–4.59 (2H, m), 6.89 (2H, d, *J* 8.7 Hz), 7.29 (2H, d, *J* 8.7 Hz), 7.38–7.41 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.1, 55.1, 55.2, 70.3, 82.1, 113.7, 127.1, 128.2, 128.5, 129.3, 130.0, 138.1, 159.1. Elemental analysis (%) calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71%; Found: C, 75.68; H, 6.84%.

(1*R*,2*R*)-Ethyl-2-((*R*)-(4-methoxybenzyloxy)(phenyl)methyl)-cyclopropanecarboxylate (3c)

To a suspension of sodium hydride (1.33 g, 33.29 mmol, 60% in mineral oil) in toluene (30 mL) was added triethylphosphonoacetate (8.8 mL, 44.36 mmol) dropwise over 15 min. After stirring at room temperature, epoxide **1c** (3 g, 11.09 mmol) in 20 mL of toluene was added dropwise over 10 min, followed by heating at 80 °C for 8 h and then temperature was raised up to 110 °C for 6 h. The solution was cooled to room temperature, diluted with ethyl acetate (50 mL), then washed with saturated aqueous ammonium chloride (50 mL). After drying over Na_2SO_4 and concentration *in vacuo*, the crude material was purified by flash chromatography using petroleum ether–EtOAc (96 : 4), to yield the desired cyclopropane carboxylate **3c** (2.83 g, 75% yield) as a thick colorless oil. $[\alpha]_D^{25}$ +9.3 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 2927, 2957, 2855, 1729, 1624, 1456, 1375, 1215, 1027, 759, 669; ^1H NMR (400 MHz, $CDCl_3$): δ 1.10–1.27 (5H, m), 1.69–1.85 (2H, m), 3.82 (3H, s), 4.08 (2H, q, *J* 2.1, 7.2 Hz), 4.2 (2H, ABq, *J* 11.2 Hz), 4.46 (1H, d, *J* 4.2 Hz), 6.7 (2H, d, *J* 8.2 Hz), 7.22–7.40 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.6, 14.2, 17.5, 27.9, 55.2, 60.4, 69.8, 71.4, 76.4, 77.6, 79.7, 113.7, 127.0, 128.5, 129.2, 129.4, 130.2, 140.8, 159.1, 173.9; MS(ESI): *m*/*z* 363.30 $(M + Na)^+$; HRMS (EI/DIP) for (M^+): calcd 340.14909, Found: 340.1437.

(1*R*,2*R*)-Ethyl 2-((*R*)-hydroxy(phenyl)methyl)cyclopropane-carboxylate (20)

To a stirring solution of PMB ether **3c** (2 g, 5.87 mmol) in CH_2Cl_2–H_2O (20 : 1) was added DDQ (2.66 g, 11.75 mmol). The resulting mixture was stirred for 3 h at 0 °C. The mixture was poured into saturated aqueous $NaHCO_3$ and further diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The solvents were removed under reduced pressure to give the crude product mixture as a yellow oil. Silica gel column chromatography of the crude product using petroleum ether–EtOAc (8 : 2) as the eluent gave **20** (1.09 g, 85% yield) as a colorless solid. $[\alpha]_D^{25}$ +11.9 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3343, 3012, 1612, 1514, 1465, 1249, 1035; ^1H NMR (200 MHz, $CDCl_3$): δ 1.13–1.20 (1H, m), 1.22–1.29 (4H, m), 1.68–2.05 (3H, m), 4.09 (2H, q, *J* 6.5 Hz), 4.51 (1H, d, *J* 6.5 Hz), 7.33–7.40 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.2, 14.1, 17.7, 28.4, 60.5, 73.9, 126, 127.8, 142.8, 173.8; HRMS (EI/DIP) for (M^+): calcd 220.10705, Found: 220.10574.

(1*R*,2*R*)-2-((*S*)-Azido(phenyl)methyl)cyclopropanecarboxylic acid (21)

To the ester **15** (400 mg, 1.63 mmol) dissolved in MeOH (10 mL) and H_2O (6.67 mL) was added $LiOH{\cdot}H_2O$ (205 mg, 4.89 mmol) and stirred at 0 °C to room temperature for 5 h. The reaction mixture was further diluted with H_2O (5 mL) and stirred for 30 min, then concentrated by a rotary evaporator to a quarter of its volume. The mixture was acidified with 1 M HCl (pH 3) and the reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (2 × 10 mL) and dried over anhydrous Na_2SO_4, filtered, evaporated and the crude product was purified by column chromatography using petroleum ether–EtOAc (7 : 3) as the eluent to give **21** (255 mg, 82% yield) as a pale yellow color syrupy liquid. $[\alpha]_D^{25}$ −13.2 (*c* 0.36, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3032, 2862, 2100, 1700, 1601, 1455, 1431, 1290, 1229, 1161, 1074, 738, 700; ^1H NMR (400 MHz, $CDCl_3$): δ 1.06–1.41 (2H, m), 1.68–2.03 (2H, m), 4.31 (1H, d, *J* 6.5 Hz), 7.13–7.47 (5H, m), 10.05 (1H, brs); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.1, 13.8, 26.9, 66.1, 126.9, 128.7, 128.9, 138.1, 179.6. Elemental analysis (%) calcd for $C_{11}H_{11}N_3O_2$: C, 75.75; H, 12.71; N, 7.62%; Found: C, 75.87; H, 12.48; N, 7.91%.

(1*R*,2*R*)-2-((*S*)-Amino(carboxy)methyl)cyclopropanecarboxylic acid (14)

Compound **21** (100 mg, 0.460 mmol) was dissolved in a mixture of CCl_4 (4 mL), CH_3CN (4 mL) and distilled H_2O (8 mL). The vigorously stirred mixture was heated to reflux temperature. Subsequently $NaIO_4$ (2.95 g, 13.8 mmol) and fresh $RuCl_3$ hydrate (14 mg, 0.069 mmol) were added. The colour changed from black *via* orange to yellow within 2 min, after which the heterogeneous mixture was poured into a mixture of DCM and ice water (1 : 1). After stirring for 30 min, the pH of the mixture was adjusted to 10 with aq. NaOH (3 M) and the mixture was extracted with DCM. The aq. layer was acidified with conc. HCl (pH < 3) and extracted with EtOAc (10 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to diacid **22** as a brown color syrupy liquid. This was directly used for the next step.

To a solution of **22** (60 mg, 0.324 mmol) in methanol (4 mL) was added in portions 10% $Pd(OH)_2$ (10 mg, 0.0810 mmol), and the mixture was hydrogenated under H_2 and at room temperature for 2–2.5 h. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was dissolved in water and purified on Amberlite CG-50 resin (NH_4^+ form), eluting with 1.5% aq. NH_4OH to furnish **14** (52 mg, 72% yield) as a colorless crystalline solid. M.p. 255–256 °C; [lit.[22c] M.p. 255–258 °C], $[\alpha]_D^{25}$ −19.7 (*c* 0.51, H_2O), {lit.:[22c] $[\alpha]_D^{25}$ −20.2 (*c* 0.51, H_2O)}; ^{1}H NMR (500 MHz, D_2O): δ 1.22 (1H, ddd, *J* 5.0, 6.3, 8.9 Hz), 1.36 (1H, ddd, *J* 5.0, 4.9, 8.9 Hz) 1.84 (1H, dddd, *J* 4.1, 6.3, 8.9, 8.9 Hz), 2.01 (1H, ddd, *J* 5.0, 4.9, 8.9 Hz), 3.55 (1H, d, *J* 9.8 Hz); ^{13}C NMR (125 MHz, D_2O): δ 13.5, 19.5, 21.9, 56.8, 172.4, 177.3.

Acknowledgements

A. D. thanks CSIR New Delhi and A. H. thanks UGC New Delhi for senior research fellowships. Financial support from DST, New Delhi (grant no. SR/S1/OC-44/2009) is gratefully acknowledged. We would like to thank Mrs S. S. Kunte for HPLC analysis.

References

1 (*a*) W. H. Gerwick, P. J. Proteau, D. G. Nagle, E. Hamel, A. Blokhin and D. L. Slates, *J. Org. Chem.*, 1994, **59**, 1243; (*b*) F. Brackmann and A. de Meijere, *Chem. Rev.*, 2007, **107**, 4493; (*c*) L. A. Wessjohann, W. Brandt and T. Thiemann, *Chem. Rev.*, 2003, **103**, 1625; (*d*) W. A. Donaldson, *Tetrahedron*, 2001, **57**, 8589.
2 (*a*) C. A. Carson and M. A. Kerr, *Chem. Soc. Rev.*, 2009, **38**, 3051; (*b*) M. Rubin, M. Rubina and V. Gevorgyan, *Chem. Rev.*, 2007, **107**, 3117.
3 (*a*) S. R. Goudreau and A. B. Charette, *Angew. Chem., Int. Ed.*, 2010, **49**, 486; (*b*) H. Pellissier, *Tetrahedron*, 2008, **64**, 7041; (*c*) E. M. McGarrigle, E. L. Myers, O. Illa, M. A. Shaw, S. L. Riches and V. K. Aggarwal, *Chem. Rev.*, 2007, **107**, 5841; (*d*) G. Maas, *Chem. Soc. Rev.*, 2004, **33**, 183; (*e*) H. Lebel, J. F. Marcoux, C. Molinaro and A. B. Charette, *Chem. Rev.*, 2003, **103**, 977; (*f*) *Comprehensive Asymmetric Synthesis*, ed. I. Ojima, Wiley-VCH Inc., New York, 2nd edn, 2000, p. 864; (*g*) M. P. Doyle and D. C. Forbes, *Chem. Rev.*, 1998, **98**, 911.
4 For reviews on this topic see: (*a*) H. M. L. Davies and E. Antoulinakis, *Org. React.*, 2001, **57**, 1; (*b*) T. Rovis and D. A. Evans, *Prog. Inorg. Chem.*, 2001, **50**, 4; (*c*) H. Nishiyama, *Enantiomer*, 1999, **4**, 569; (*d*) V. K. Singh, A. Datta Gupta and G. Shekhar, *Synthesis*, 1997, 137.
5 H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, 1959, **81**, 4256.
6 E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1353.
7 O. G. Kulinkovich and A. de Merijere, *Chem. Rev.*, 2000, **100**, 2789.
8 For selected examples, see: (*a*) I. Artaud, J. Seyden-Penne and P. Viout, *Synthesis*, 1980, 34; (*b*) T. Hudlicky, L. Radesca, H. Luna and F. E. Anderson, *J. Org. Chem.*, 1986, **51**, 4746; (*c*) K. Hakam, M. Thielmann, T. Thielmann and E. Winterfeldt, *Tetrahedron*, 1987, **43**, 2035; (*d*) I. Shibata, Y. Mori, H. Yamasaki, A. Baba and H. Matsuda, *Tetrahedron Lett.*, 1993, **34**, 6567; (*e*) N. A. Rodios, A. Bojilova, A. Terzis and C. P. Raptopoulou, *J. Heterocycl. Chem.*, 1994, **31**, 1129; (*f*) F. Cluet, A. Haudrechy, P. Leber, P. Sinay and A. Wick, *Synlett*, 1994, 913; (*g*) K. Badiani, P. Lightfoot and D. Gani, *Chem. Commun.*, 1996, 675; (*h*) T. F. Braish, M. Castaldi, S. Chan, D. E. Fox, T. Keltonic, J. McGarry, J. M. Hawkins, T. Norris, P. R. Rose, J. E. Sieser, B. J. Sitter and H. Watson Jr., *Synlett*, 1996, 1100; (*i*) V. Calo, A. Nacci, L. Lopez and V. L. Lerario, *Tetrahedron Lett.*, 2000, **41**, 8977; (*j*) A. Escribano, C. Pedregal, R. González, A. Fernandez, K. Burton and G. A. Stephenson, *Tetrahedron*, 2001, **57**, 9423; (*k*) S. S. Bhattacharjee, H. Ila and H. Junjappa, *Synthesis*, 1982, 301; (*l*) N. Ono, T. Yanai, I. Hamamoto, A. Kamimura and A. Kaji, *J. Org. Chem.*, 1985, **50**, 2806; (*m*) D. Caine, *Tetrahedron*, 2001, **57**, 2643; (*n*) J. Li, Y.-C. Liu and J.-G. Deng, *Tetrahedron: Asymmetry*, 1999, **10**, 4343.
9 (*a*) N. Bremeyer, S. C. Smith, S. V. Ley and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2004, **43**, 2681; (*b*) C. D. Papageorgious, M. A. Cubillo de Dios, S. V. Ley and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2004, **43**, 4641; (*c*) R. K. Kunz and D. W. C. Macmillan, *J. Am. Chem. Soc.*, 2005, **127**, 3240.
10 For a recent example, see: P. L. Beaulieu, J. Gillard, M. D. Bailey, C. Boucher, J.-S. Duceppe, B. Simoneau, X.-J. Wang, L. Zhang, K. Grozinger, I. Houpis, V. Farina, H. Heimroth, T. Krueger and J. Schnaubelt, *J. Org. Chem.*, 2005, **70**, 5869.
11 W. S. Wadsworth and W. D. Emmons, *J. Am. Chem. Soc.*, 1961, **83**, 1733.
12 (*a*) L. Delhaye, A. Merschaert, P. Delbeke and W. Brione, *Org. Process Res. Dev.*, 2007, **11**, 689; (*b*) M. Khurram, N. Qureshi and M. D. Smith, *Chem. Commun.*, 2006, 5006; (*c*) A. Armstrong and J. N. Scutt, *Chem. Commun.*, 2004, 510; (*d*) A. Armstrong and J. N. Scutt, *Org. Lett.*, 2003, **5**, 2331; (*e*) A. K. Singh, M. N. Rao, J. H. Simpson, W. S. Li, J. E. Thornton, D. E. Kuehner and D. J. Kacsur, *Org. Process Res. Dev.*, 2002, **6**, 618; (*f*) T. E. Jacks, H. Nibbe and D. F. Wiemer, *J. Org. Chem.*, 1993, **58**, 4584; (*g*) R. C. Petter, S. Banerjee and S. Englard, *J. Org. Chem.*, 1990, **55**, 3088; (*h*) R. C. Petter, *Tetrahedron Lett.*, 1989, **30**, 399; (*i*) B. J. Fitzsimmons and B. Fraser-Reid, *Tetrahedron*, 1984, **40**, 1279; (*j*) R. G. Ghirardelli, *J. Am. Chem. Soc.*, 1973, **95**, 4987; (*k*) R. A. Izydore and R. G. Ghiradelli, *J. Org. Chem.*, 1973, **38**, 1790; (*l*) I. Tömösközi, *Tetrahedron*, 1966, **22**, 179; (*m*) D. B. Denney, J. J. Vill and M. J. Boskin, *J. Am. Chem. Soc.*, 1962, **84**, 3944; (*n*) T. Meul, P. Weinhold and A. G. Lonza, *Eur. Pat.*, 491330, 1992; (*o*) D. L. J. Clive and S. Daigneault, *J. Chem. Soc., Chem. Commun.*, 1989, 332; (*p*) J. A. Robl, E. Sieber-McMaster and R. Sulsky, *Tetrahedron Lett.*, 1996, **37**, 8985; (*q*) V. Padmavati, K. Sharmila, A. S. Reddy and D. B. Reddy, *Ind. J. Chem. B.*, 2001, **40**, 11.
13 (*a*) C. D. Bray and F. Minicone, *Chem. Commun.*, 2010, **46**, 5867; (*b*) C. D. Bray and G. D. Faveri, *J. Org. Chem.*, 2010, **75**, 4652.
14 The assignment of the *trans* relationship between the R-group and ester of **3a** and **3b** was based on ^{1}H NMR spectroscopy where the methylene hydrogen of ester functionality resonated with a highly diagnostic downfield chemical shift of >4 ppm. According to the literature report, the methylene proton of the *cis* compound is known to exhibit an upfield shift to 3.74; for a detailed explanation to distinguish *cis* and *trans*-cyclopropyl ester, see the ESI† of: P. Panne, A. DeAnglesi and J. M. Fox, *Org. Lett.*, 2008, **10**, 2987.
15 Enantioselectivity of cyclopropyl esters was determined by HPLC: Chiralcel OD-H column (2-propanol–petroleum ether = 0.15 : 99.85, flow rate 0.5 mL min^{-1} for **3b**), Chiralcel OD-H column (ethanol–*n*-hexane = 05 : 95, flow rate 0.5 mL min^{-1} for **3c**). The ee of **3a** is based on comparison of the optical rotation with the reported value.
16 (*a*) V. Jha, N. B. Kondekar and P. Kumar, *Org. Lett.*, 2010, **12**, 2762; (*b*) P. Kumar, P. Gupta and S. V. Naidu, *Chem.–Eur. J.*, 2006, **12**, 1397; (*c*) P. Kumar, S. V. Naidu and P. Gupta, *J. Org. Chem.*, 2005, **70**, 2843; (*d*) P. Kumar and S. V. Naidu, *J. Org. Chem.*, 2005, **70**, 4207; (*e*) P. Kumar and S. V. Naidu, *J. Org. Chem.*, 2006, **71**, 3935; (*f*) P. Gupta and P. Kumar, *Eur. J. Org. Chem.*, 2008, 1195; (*g*) P. Kumar, M. Pandey, P. Gupta, S. V. Naidu and D. D. Dhavale, *Eur. J. Org. Chem.*, 2010, 6993; (*h*) A. Dubey, V. G. Puranik and P. Kumar, *Org. Biomol. Chem.*, 2010, **8**, 5074 and references cited therein.
17 (*a*) I. O. Roberts, M. S. Baird and Y. Liu, *Tetrahedron Lett.*, 2004, **45**, 8685; (*b*) M. Cheeseman and S. D. Bull, *Synlett*, 2006, 1119; (*c*) M. Cheeseman, I. R. Davies, P. Axe, A. L. Johnson and S. D. Bull, *Org. Biomol. Chem.*, 2010, **8**, 5074; (*d*) S. R. Wilson and K. A. Prodan, *Tetrahedron Lett.*, 1976, **47**, 4231; (*e*) T. D. Hartog, A. Rudolph, B. Macia, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc.*, 2010, **132**, 14349.
18 N. Sitachitta and W. H. Gerwick, *J. Nat. Prod.*, 1998, **61**, 681.
19 (*a*) J. R. A. Dulayymi, M. S. Baird and K. Jones, *Tetrahedron*, 2004, **60**, 341; (*b*) R. Green, M. Cheessman, S. Duffill, A. Merritt and S. D. Bull, *Tetrahedron Lett.*, 2005, **46**, 7931; (*c*) T. D. Avery, J. A. Culbert and D. K. Taylor, *Org. Biomol. Chem.*, 2006, **4**, 323; (*d*) T. Minuth and M. M. K. Boysen, *Synthesis*, 2010, 2799.
20 C. J. Kowalski, M. S. Haque and K. W. Fields, *J. Am. Chem. Soc.*, 1985, **107**, 1429.
21 (*a*) K. Shimamoto and Y. Ohfune, *J. Med. Chem.*, 1996, **39**, 407; (*b*) P. L. Ornstein, T. J. Bleisch, M. B. Arnold, R. A. Wright, B. G. Johnson and D. D. Schoepp, *J. Med. Chem.*, 1998, **41**, 346; (*c*) P. L. Ornstein, T. J. Bleisch, M. B. Arnold, J. H. Kennedy, R. A. Wright, B. G. Johnson, J. P. Tizzano, D. R. Helton, M. J. Kallman and D. D. Schoepp, *J. Med. Chem.*, 1998, **41**, 358; (*d*) K. Yamanoi, Y. Ohfune, K. Watanabe, P. N. Li and H. Takeuchi, *Tetrahedron Lett.*, 1988, **29**, 1181.
22 For racemic synthesis of CCG-II, see: (*a*) S. P. Chavan, M. S. Venkatraman, A. K. Sharma and A. G. Chittiboyina, *Tetrahedron*

Lett., 1996, **37**, 2857; (*b*) M. Yamaguchi, K. Torisu and T. Minami, *Chem. Lett.*, 1990, 377; For asymmetric synthesis of L-(−) CCG-II, see: (*c*) K. Shimamoto, M. Ishida, H. Shinozaki and Y. Ohfune, *J. Org. Chem.*, 1991, **56**, 4167.
23 (*a*) G. Li, H.-T. Chang and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 451; (*b*) H. C. Kolb, M. S. VanNiewenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.
24 E. Lallana, F. Freire, J. M. Seco, E. Quiñoá and R. Riguera, *Org. Lett.*, 2006, **8**, 4449.
25 M. J. Martinelli, R. Vaidyanathan, J. M. Pawlak, N. K. Nayyar, U. P. Dhokte, C. W. Doecke, L. M. H. Zollars, E. D. Moher, V. V. Khau and B. Kosmrlj, *J. Am. Chem. Soc.*, 2002, **124**, 3578.
26 R. V. A. Orru, I. Osprian, W. Kroutil and K. Faber, *Synthesis*, 1998, 1259.

