Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: R. A. Fernandes and J. L. Nallasivam, *Org. Biomol. Chem.*, 2016, DOI: 10.1039/C6OB02398C.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C6OB02398C

Journal Name

ARTICLE

A Protecting-Group-Free Synthesis of (+)-Nephrosteranic, (+)-Protolichesterinic, (+)-Nephrosterinic, (+)-Phaseolinic, (+)-Rocellaric Acids and (+)-Methylenolactocin‡

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Jothi L. Nallasivam and Rodney A. Fernandes*

A collective synthesis of γ-butyrolactone class of paraconic acids such as (+)-methylenolactocin, (+)-phaseolinic acid, (+)-nephrosteranic acid, (+)-nephrosterinic acid, (+)-rocellaric acid and (+)-protolichesterinic acid is described. The strategy adopted is protecting-group-free based on an efficient Pd-catalyzed Suzuki–Miyaura coupling and Ru-catalyzed Sharpless oxidation to construct the core β-CO_2H-γ-butyrolactone unit to accomplish the synthesis of various paraconic acids.

Introduction

γ-Butyrolactone and γ-butenolide are core structural motifs in many natural products and pharmaceuticals possessing potential biological activities.[1] For example, the γ-butyrolactone unit is embedded in various paraconic acids (**1**–**10**, Figure 1).[2] These were isolated from lichens, various species of moss and culture filtrates of *penicillium sp*.[3] The γ-butyrolactones are equivalent to 4-hydroxycarbonyl compounds[4] which are functionalized at the ring carbons and show interesting bioactivities such as antibacterial,[5a,b] antiviral/antifungal,[5c] antibiotic,[5d,e] antitumor and growth regulatory properties.[5f] The molecular architecture of paraconic acids is accompanied by (a) the presence of C4-CO_2H functionality and C5-alkyl side-chain of variable length and (b) C3-substituent, either methyl or methylene unit, which plays prominent roles in determining the physiological properties of a particular class of paraconic acids.[5] Several new glycosides have been isolated with paraconic acids as the aglycon components.[6] The interesting bioactivities have prompted many researchers to devise distinct synthetic routes toward these natural products. A number of total[7] and formal[8] syntheses have been reported for paraconic acids such as (+)-methylenolactocin, (+)-phaseolinic acid, (+)-nephrosteranic acid, (+)-nephrosterinic acid, (+)-rocellaric acid and (+)-protolichesterinic acid in racemic as well as in enantiopure forms. The strategies adopted for the enantioselective synthesis of these paraconic acids include π-face differentiation in chiral olefin-ketene [2+2] cycloaddition,[5d,7b] Cu-catalyzed cyclopropanation,[7p] regioselective asymmetric dihydroxylation,[7s] asymmetric epoxidation,[7d,f,ab,] asymmetric reduction of β-keto esters,[7w] chiral conjugate additions,[7t] asymmetric allylic alkylation,[7ac,ad] chemoenzymatic resolution,[7i] use of chiral auxiliaries,[7h,l,m,x,ae] chiral synthons[7c,e,o] and chiral pool approaches.[7j,n,q,r,y] While the syntheses are competitively achieved, some suffer from large number of steps involved and lower overall yields. Thus there is a need to design a strategy which is step-economic and protecting-group-free toward achieving the goal of an ideal synthesis.

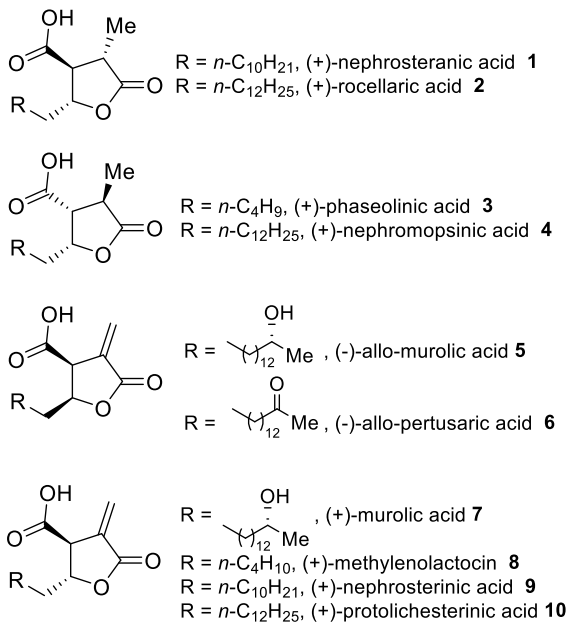


Figure 1. γ-Butyrolactone based paraconic acids.

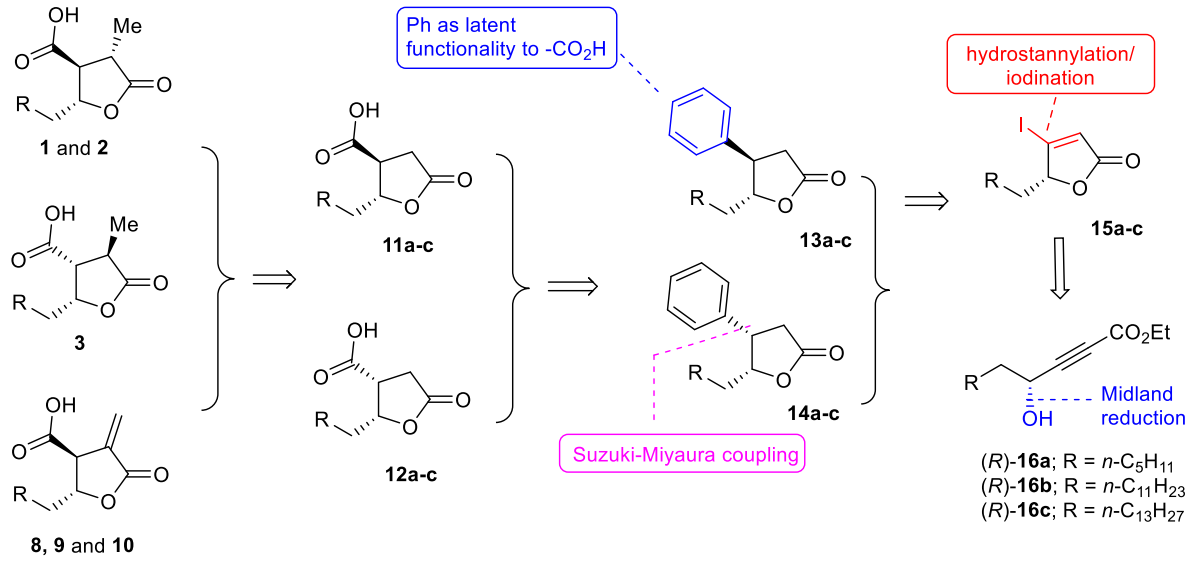
Department of Chemistry, Indian Institute of Technology Bombay,
Powai, Mumbai 400 076, Maharashtra, India.
E-mail: rfernand@chem.iitb.ac.in; Fax: +91 22 25767152;
Tel: +91 22 25767174

‡ Electronic supplementary information (ESI) available: Copies of HPLC chromatograms, ^{1}H NMR and ^{13}C NMR spectra for all the compounds.

View Article Online
DOI: 10.1039/C6OB02398C

Journal Name

ARTICLE



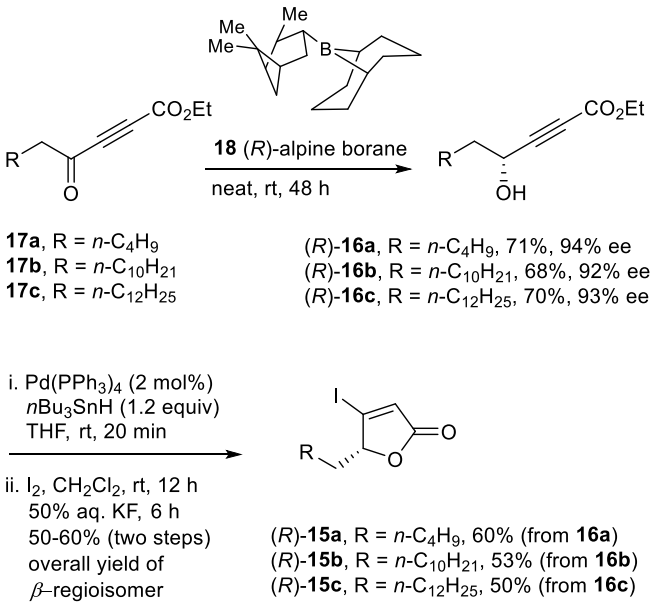
Scheme 1. Retrosynthetic route to paraconic acids.

Recently, we reported the stereoselective synthesis of paraconic acids by regioselective asymmetric dihydroxylation and Johnson–Claisen rearrangement.[9] Our interest lies in designing enantioselective synthetic routes to access γ-butyrolactone/γ-butenolide derived bioactive natural products[10] with emphasis on step-economy and protecting-group-free approaches. In this article, we describe an efficient Suzuki–Miyaura coupling using the ligand[11] developed in our laboratory and an oxidative phenyl group to carboxylic acid transformation for the collective synthesis of various paraconic acids. The scope of Suzuki–Miyaura coupling between butenolide-derived vinyliodide and boronic acids is less realized and application to paraconic acid synthesis is hitherto unknown.

Results and Discussion

The retrosynthetic route to access paraconic acids is depicted in Scheme 1. The key element of our approach is to assemble the *anti*- and *syn*-phenyl butyrolactones **13** and **14** respectively, without involvement of protecting groups. The phenyl group was easy to install via the Suzuki-Miyaura (SM) coupling and serves as latent functionality to the desired β-CO_2H group (Ru-mediated oxidative cleavage under Sharpless conditions[13]) in the target molecules via **11** or **12**. The vinyliodide-butenolide moiety **15** for SM coupling was planned from γ-hydroxy-2-alkynoate **16** by hydrostannylation/iodination. The chiral alkynol **16** can be prepared by chiral reduction of the corresponding keto group.

The forward synthesis was executed with the preparation of chiral alkynols **16** from ketones **17** *via* Midland[14] reduction employing (*R*)-alpine borane **18** (Scheme 2). The enantiomeric excesses of alkynols was determined for **16a** = 94% ee, **16b** = 92% ee and **16c** = 93% ee by converting them into their respective *p*-nitrobenzoate derivatives.[15] The alkynols **16** upon $Pd(PPh_3)_4$-catalyzed hydrostannylation with nBu_3SnH followed

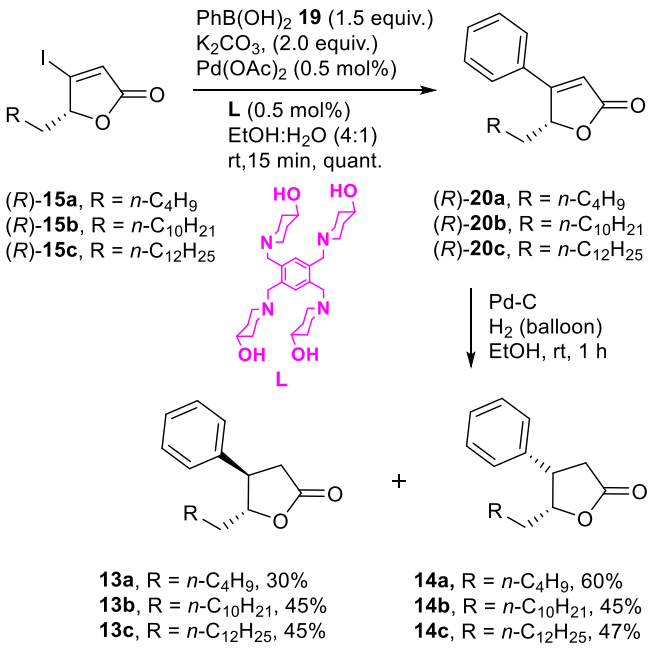


Scheme 2. Synthesis of β-iodo-butenolides **15**.

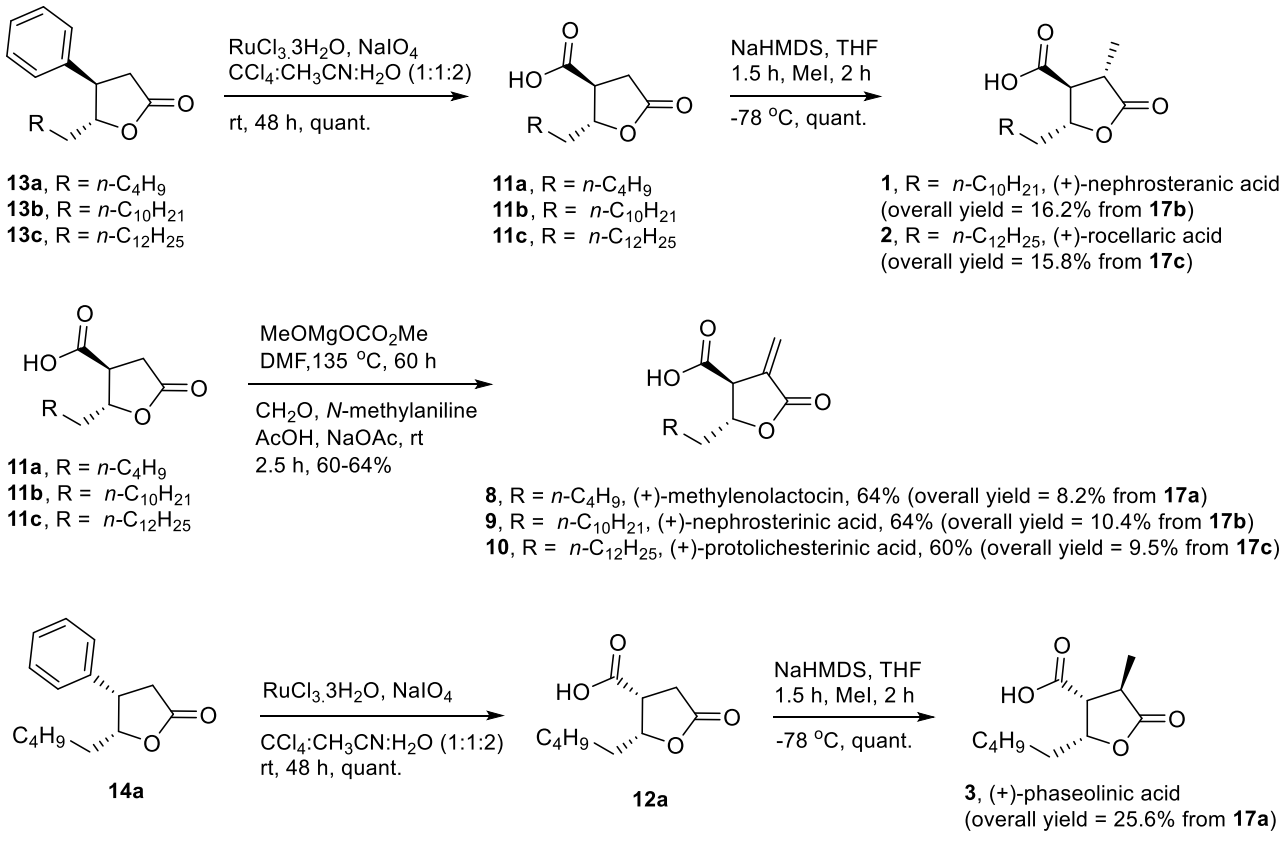
View Article Online
DOI: 10.1039/C6OB02398C

by lactonization delivered the regioisomeric mixture of vinyl-stannane intermediates. Interestingly, the concentration and rate of addition of nBu$_3$SnH could switch the regioselectivity pattern. A dilute reaction and slow addition of nBu$_3$SnH to alkynol **16** furnished the α-stannane butenolide (α:β = 2−5:1) as the major regioisomer. However, higher reaction concentration and fast addition of nBu$_3$SnH to alkynol **16** delivered β-stannane butenolide (α:β = 1:3) as the major regioisomer. As an added advantage, the regioisomers could be separated by column chromatography prior to vinyliodide synthesis. The intermediate β-stannane was treated with molecular I_2 to provide β-iodobutenolides **15a-c** (Scheme 2) in overall 50-60% yield from **16** via the intermediate β-stannane regioisomers.

The Suzuki–Miyaura coupling of β-iodobutenolides **15a-c** with PhB(OH)$_2$ was efficiently executed under our previously optimized procedure using the ligand **L**[11] developed in our laboratory (Scheme 3). This delivered β-phenylbutenolides **20a-c** in quantitative yields. The reaction required only 0.5 mol% each of Pd(OAc)$_2$ and the ligand **L**. The heterogenous hydrogenation of **20a-c** in the presence of Pd-C (10% w/w) under H_2 (1 atm) furnished β-phenylbutyrolactones (**13/14**) in quantitative yields as *anti*:*syn* diastereomeric mixture (*anti:syn* = 1:1.2-2). Although the diastereoselectivity was not satisfactory, the *syn*-isomer predominates and the mixture can be separated efficiently by column chromatography.



Scheme 3. Synthesis of β-phenyl butyrolactones **13** and **14**.



Scheme 4. Synthesis of (+)-nephrosteranic acid, (+)-rocellaric acid, (+)-methylenolactocin, (+)-nephrosterinic acid, (+)-protolichesterinic acid and (+)-phaseolinic acid.

View Article Online
DOI: 10.1039/C6OB02398C

Journal Name

ARTICLE

Upon oxidative cleavage of β-phenyl-moiety in **13** under Sharpless oxidative protocol[13] using $RuCl_3.3H_2O/NaIO_4$, it furnished β-CO_2H-*γ*-butyrolactones **11** in quantitative yields (Scheme 4). The C4-phenyl group in γ-butenolides **20** thus served as latent functionality to install β-CO_2H functional group. The α-methylation[7n] (NaHMDS/MeI/THF) of **11b** and **c** delivered (+)-nephrosteranic acid **1** and (+)-rocellaric acid **2**, respectively in quantitative yields. The α-methylenation of **11a-c** (using Stiles reagent)[16] efficiently provided (+)-methylenolactocin **8**, (+)-nephrosterinic acid **9** and (+)-protolichesterinic acid **10** (Scheme 4) respectively in good yields (60-64%). The *syn*-butyrolactone **14a** on oxidative cleavage of phenyl group gave the β-CO_2H butyrolactone **12a** quantitatively. Further α-methylation completed the synthesis of (+)-phaseolinic acid **3** in quantitative yield.[7i] The spectral data of all synthesized paraconic acids matched well with literature data.[7c,i,l,s]

Conclusions

In conclusion, we have developed a highly concise and collective synthesis of various paraconic acids, (+)-methylenolactocin, (+)-phaseolinic acid, (+)-nephrosteranic acid, (+)-nephrosterinic acid, (+)-rocellaric acid and (+)-protolichesterinic acid by Pd-mediated efficient Suzuki–Miyaura cross coupling followed by oxidative cleavage of β-phenyl group to afford the advanced β-CO_2H butyrolactone intermediates. The easy installation of β-phenyl group by Suzuki-Miyaura coupling and its subsequent oxidation to β-CO_2H group are key features in the synthesis. The stereoselective α-methylation or methylenation completed the syntheses of various paraconic acids. Thus, an efficient collective protecting-group-free synthesis of various paraconic acids in high overall yields is demonstrated. The strategy has potential for the synthesis of other members of the paraconic acid family, shown in Figure 1.

Experimental Section

General Information: Solvents were dried by standard procedures. Thin-layer chromatography was performed on EM 250 Kieselgel 60 F254 silica gel plates. The spots were visualized by staining with $KMnO_4$ or by using UV lamp. ^{1}H-NMR and ^{13}C-NMR were recorded with a spectrometer operating at 400 or 500 and 100 or 125 MHz for proton and carbon nuclei, respectively. The chemical shifts are based on TMS peak at δ = 0.00 pm for proton NMR and $CDCl_3$ peak at δ = 77.00 ppm (t) in carbon NMR. For other deuterated solvents the standard chemical shifts were considered. IR spectra were obtained on an FT-IR spectrometer. Optical rotations were measured using Sodium D line (589 nm). HRMS were recorded using positive electrospray ionization by the TOF method. The enantiomeric excess of the alkynol was determined by HPLC method using chiral columns, Chiralpak IA and IC at wavelength 254 nm.

General procedure for the synthesis of alkynols (16a-c):[14] A solution of (*R*)-alpine borane **18** (6 mL, 0.5M in THF, 3.0 mmol, 2.0 equiv.) was charged into a round-bottom flask followed by dropwise addition of a solution of acetylenic ketones **17a-c** (1.5 mmol) in THF (3.0 mL) at 0 °C. The solvent was removed under vacuum to render a neat reaction mixture. The reaction flask was flushed with N_2 and stirred for 48 h at room temperature. Excess alpine-borane was destroyed by adding freshly distilled propionaldehyde (1.0 mmol) and stirred for 1 h at room temperature. The reaction mixture was dissolved in THF (3.0 mL) and then treated with aqueous 3M NaOH (2.0 mL). Then 30% H_2O_2 (2.0 mL) was added dropwise at 0 °C and stirred for 4 h at 40 °C. The reaction mixture was extracted with Et_2O (3 × 15 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated. The crude residue was purified by column chromatography using petroleum ether/EtOAc (9:1) as eluent to afford alkynols **16a-c** in good yields (68-71%).

General procedure for the synthesis of *p*-nitrobenzoate derivatives of 16a-c: To a solution of alkynols **16a-c** (0.1 mmol) in dry CH_2Cl_2 (5.0 mL) were added Et_3N (20.9 mg, 0.15 mmol) and *p*-nitrobenzoyl chloride (22.3 mg, 0.12 mmol) at 0 °C. After 30 min, the reaction mixture was quenched with few drops of water and concentrated to afford a brown residue. The residue was purified by column chromatography using petroleum ether/EtOAc (20:1) as eluent to afford *p*-nitrobenzoate derivatives of **16a-c**.

Alkynol 16a: Yield (211 mg, 71%); colorless oil; $[\alpha]_D^{25}$ = 23.5 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.7 Hz, 3H), 1.10−1.40 (m, 7H), 1.40−1.60 (m, 2H), 1.70−1.90 (m, 2H), 2.09 (brs, 1H, *OH*), 4.24 (q, *J* = 7.2 Hz, 2H), 4.48 (t, *J* = 6.7 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 14.0, 22.4, 24.6, 31.3, 36.8, 62.1, 62.2, 76.5, 87.9, 153.5 ppm. IR ($CHCl_3$): ν_{max} = 3419, 2958, 2934, 2863, 2238, 1715, 1467, 1368, 1248, 1020, 861, 752, 636 cm^{-1}. HRMS (ESI−TOF): calcd for $[C_{11}H_{18}O_3+H]^+$ 199.1334, found 199.1340. The alcohol was converted into *p*-nitrobenzoate derivative for HPLC analysis. HPLC: Chiralpak IC, *n*Hexane/IPA = 90:10, flow rate = 1 mL/min, t_R = 11.16 min (major) min, t_R = 10.58 min (minor), *ee* = 94%.

***p*-Nitrobenzoate derivative of 16a:** Yield (32.9 mg, 95%); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.8 Hz, 3H), 1.24−1.38 (m, 7H), 1.51−1.58 (m, 2H), 1.96−2.02 (m, 2H), 4.21 (q, *J* = 7.2 Hz, 2H), 5.70 (t, *J* = 6.4 Hz, 1H), 8.22 (d, *J* = 9.2 Hz, 2H), 8.30 (d, *J* = 8.8 Hz, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.85, 13.9, 22.3, 24.5, 31.1, 33.9, 62.3, 64.7, 77.4, 83.1, 123.6, 130.9, 134.6, 150.7, 152.9, 163.4 ppm. IR ($CHCl_3$): ν_{max} = 3114, 2958, 2931, 2863, 2245, 1717, 1607, 1531, 1465, 1409, 1347, 1320, 1247, 1098, 1014, 906, 872, 839, 783, 720 cm^{-1}. HRMS (ESI−TOF): calcd for $[C_{18}H_{21}NO_6+H]^+$ 348.1447, found 348.1450.

Alkynol 16b: Yield (288 mg, 68%); colorless oil; $[\alpha]_D^{25}$ = 31.5 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.9 Hz, 3H), 1.0−1.40 (m, 19H), 1.41−1.47 (m, 2H), 1.72−1.79 (m, 2H), 2.02 (brs, 1H, *OH*), 4.24 (q, *J* = 7.1 Hz, 2H), 4.48 (t, *J* = 6.7 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 14.1, 22.7, 24.9, 29.1, 29.3, 29.4, 29.5, 29.6, 31.9, 36.9, 62.1, 62.14, 76.5, 87.9, 153.4 ppm. IR ($CHCl_3$): ν_{max} = 3441, 3020, 2929, 2857, 2239, 1968, 1714, 1639, 1467, 1369, 1259, 1021, 933, 768, 669 cm^{-1}. HRMS (ESI−TOF): calcd for $[C_{17}H_{30}O_3+H]^+$ 283.2274, found 283.2279. The alcohol was converted into *p*-nitrobenzoate derivative for HPLC analysis. HPLC: Chiralpak IA, *n*Hexane/IPA = (90:10), flow rate = 1 mL/min, t_R = 15.69 min (major) min, t_R = 13.05 min (minor), *ee* = 92%.

***p*-Nitrobenzoate derivative of 16b:** Yield (40.6 mg, 94%); colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 6.5 Hz, 3H), 1.23−1.34 (m, 19H), 1.49−1.55 (m, 2H), 1.97−2.02 (m, 2H), 4.22 (q, *J* = 7.0 Hz, 2H), 5.69 (t, *J* = 6.5 Hz, 1H), 8.21 (d, *J* = 8.5 Hz, 2H), 8.28 (d, *J* = 8.5 Hz, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 14.0, 22.6, 24.8, 29.0, 29.3, 29.4, 29.6, 31.8, 33.9, 62.3, 64.7, 77.4, 83.1, 123.6, 130.9, 134.7, 150.7, 152.9, 163.4 ppm. IR ($CHCl_3$): ν_{max} = 3114, 2927, 2854, 2245, 1718, 1607, 1531, 1464, 1409, 1347, 1319, 1098, 1014, 872, 852, 783, 720 cm^{-1}. HRMS (ESI−TOF): calcd for $[C_{24}H_{33}NO_6+H]^+$ 432.2387, found 432.2392.

Alkynol 16c: Yield (326 mg, 70%); pale yellow oil; $[\alpha]_D^{25}$ = 19.8 (*c* = 0.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.2 Hz, 3H), 1.25−1.33 (m, 23H), 1.42−1.48 (m, 2H), 1.73−1.81 (m, 2H), 1.98 (brs, 1H, *OH*), 4.21 (q, *J* = 7.2 Hz, 2H), 4.46 (t, *J* = 6.7 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 14.1, 22.7, 24.9, 29.1, 29.3, 29.4, 29.5, 29.6, 29.63, 29.7, 31.9, 36.9, 62.2, 76.6, 87.8, 153.4 ppm. IR ($CHCl_3$): ν_{max} = 3421, 2925, 2855, 2237, 1717, 1466, 1368, 1246, 1048, 862, 752, 723, 628 cm^{-1}. HRMS (ESI−TOF): calcd for $[C_{19}H_{34}O_3+H]^+$ 311.2586, found 311.2591. The alcohol was converted into *p*-nitrobenzoate derivative for HPLC analysis. HPLC: Chiralpak IA, *n*Hexane/IPA = (85:15), flow rate = 1 mL/min, t_R = 8.39 min (major) min, t_R = 7.07 min (minor), *ee* = 93%.

***p*-Nitrobenzoate derivative of 16c:** Yield (43.7 mg, 95%); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3H), 1.25−1.32 (m, 23H), 1.51−1.57 (m, 2H), 1.98−2.04 (m, 2H), 4.21 (q, *J* = 7.2 Hz, 2H), 5.70 (t, *J* = 6.8 Hz, 1H), 8.21 (d, *J* = 8.8 Hz, 2H), 8.29 (d, *J* = 8.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 14.1, 22.7, 24.9, 29.0, 29.3, 29.5, 29.55, 29.6, 29.63, 31.9, 34.0, 62.3, 64.8, 77.5, 83.2, 123.6, 131.0, 134.7, 150.8, 152.9, 163.4 ppm. IR ($CHCl_3$): ν_{max} = 2926, 2855, 2245, 1719, 1607, 1531, 1464, 1410, 1347, 1319, 1269, 1245, 1098, 1015, 968, 872, 853, 719 cm^{-1}. HRMS (ESI−TOF): calcd for $[C_{26}H_{37}NO_6+H]^+$ 460.2700, found 460.2694.

General procedure for the synthesis of β-iodo butenolides (15a-c): To a solution of alkynols **16a-c** (0.5 mmol) in dry THF (5.0 mL), were added $Pd(Ph_3P)_4$ (11.6 mg, 0.01 mmol, 2.0 mol%) and Bu_3SnH (175 mg, 0.6 mmol) in one portion at room temperature. After 20 min, the reaction mixture was concentrated to afford a brown residue. The regioisomeric mixture was purified by fast column chromatography using petroleum ether and EtOAc (20:1) as eluent to afford β-stannane butenolide. To a solution of this in dry CH_2Cl_2 (10 mL), was added I_2 (152.4 mg, 0.6 mmol) in dry CH_2Cl_2 dropwise at room temperature. The reaction was stirred for 12 h and then treated with 50% aq. KF solution (5 mL) and stirred for additional 6 h. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give crude vinyl iodide. The crude residue was purified by column chromatography using petroleum ether/EtOAc (19:1) as eluent to deliver β-iodo butenolides **15a-c** in 50−60% yield (two steps).

Butenolide 15a: Yield (84.0 mg, 60%); colorless oil; $[\alpha]_D^{25}$ = 12.8 (*c* = 0.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.9 Hz, 3H), 1.30−1.42 (m, 6H), 1.55−1.64 (m, 1H), 1.99−2.07 (m, 1H), 4.94−4.97 (m, 1H), 6.51 (d, *J* = 1.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.3, 23.3, 31.2, 32.4, 88.0, 125.3, 130.0, 171.1 ppm. IR ($CHCl_3$): ν_{max} = 3101, 3016, 2952, 2929, 2860, 1755, 1587, 1464, 1376, 1332, 1244, 1161, 1090, 1039, 1014, 926, 880, 853, 699 cm^{-1}. HRMS (ESI−TOF): calcd for $[C_9H_{13}O_2I+Na]^+$ 302.9858, found 302.9863.

Butenolide 15b: Yield (96.5 mg, 53%); colorless oil; $[\alpha]_D^{25}$ = 13.8 (*c* = 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 6.9 Hz, 3H), 1.25−1.43 (m, 18H), 1.53−1.65 (m, 1H), 1.99−2.07 (m, 1H), 4.94−4.97 (m, 1H), 6.51 (d, *J* = 1.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.7, 23.7, 29.1, 29.28, 29.3, 29.4, 29.6, 31.9, 32.5, 88.0, 125.3, 130.0, 171.1 ppm. IR ($CHCl_3$): ν_{max} = 2925, 2854, 1768, 1572, 1465, 1377, 1327, 1264, 1185, 987, 705 cm^{-1}. HRMS (ESI−TOF): calcd for $[C_{15}H_{25}O_2I+H]^+$ 365.0978, found 365.0987.

Butenolide 15c: Yield (98.1 mg, 50%); colorless oil; $[\alpha]_D^{25}$ = 11.3 (*c* = 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.8 Hz, 3H), 1.26−1.33 (m, 22H), 1.56−1.63 (m, 1H), 1.98−2.08 (m, 1H), 4.94−4.98 (m, 1H), 6.51 (d, *J* = 1.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.7, 23.7, 29.1, 29.29, 29.3, 29.5, 29.57, 29.6, 29.7, 31.9, 32.5, 88.0, 125.3, 130.1, 171.1 ppm. IR ($CHCl_3$): ν_{max} = 3021, 2924, 2853, 1757, 1735, 1588, 1491, 1464, 1161, 1041, 1022, 932, 911, 877, 854, 688, 669 cm^{-1}. HRMS (ESI−TOF): calcd for $[C_{17}H_{29}O_2I+K]^+$ 431.0844, found 431.0848.

General procedure for the synthesis of 4-phenylbutenolides (20a-c):[11b] To a solution of β-iodo butenolides **15a-c** (0.5 mmol) in EtOH:H_2O (4:1, 6.0 mL) were added sequentially $PhB(OH)_2$ **19** (90.8 mg, 0.750 mmol, 1.5 equiv.), K_2CO_3 (138.2 mg, 1.0 mmol, 2.0 equiv.), $Pd(OAc)_2$ (0.56 mg, 0.0025 mmol, 0.5 mol%) and ligand **L** (1.32 mg, 0.0025 mmol, 0.5 mol%). The reaction mixture was stirred at room temperature for 15 min and then filtered through a small pad of celite and washed with CH_2Cl_2 (2 × 25 mL). The filtrate was concentrated and the residue purified by column chromatography using petroleum ether/EtOAc as eluent to give 4-phenylbutenolides **20a-c** in quantitative yields.

Butenolide 20a: Yield (115.1 mg, quant.); colorless oil; $[\alpha]_D^{25}$ = −80.2 (*c* = 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.3 Hz, 3H), 1.18−1.30 (m, 4H), 1.37–1.47 (m, 2H), 1.53–1.62 (m, 1H), 1.95–2.03 (m, 1H), 5.48–5.51 (m, 1H), 6.26 (d, *J* = 1.1 Hz, 1H), 7.45–7.49 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.4, 24.2, 31.3, 33.4, 82.3, 114.3, 127.1, 129.2, 130.2, 131.2, 167.8, 172.9 ppm. IR ($CHCl_3$): ν_{max} = 2926, 2851, 1755, 1599, 1492, 1448, 1338, 1275, 1118, 1026, 963, 894, 792, 694 cm^{-1}. HRMS (ESI−TOF): calcd for $[C_{15}H_{18}O_2+H]^+$ 231.1385, found 231.1390.

Butenolide 20b: Yield (157.2 mg, quant.); colorless oil; $[\alpha]_D^{25}$ = −95.4 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.0 Hz, 3H), 1.21−1.28 (m, 16H), 1.34–1.46 (m, 2H), 1.54–1.60 (m, 1H), 1.95–2.02 (m, 1H), 5.48–5.51 (m, 1H), 6.27 (d, *J* = 1.4 Hz, 1H), 7.44–7.50 (m, 5H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 22.7, 24.5, 29.2, 29.3, 29.32, 29.4, 29.6, 31.9, 33.5, 82.3, 114.3, 127.1, 129.2, 130.2, 131.2, 167.8, 173.0 ppm. IR ($CHCl_3$): ν_{max} = 2925, 2851, 1756, 1596, 1492, 1448, 1341, 1264, 1118, 1023, 963, 891, 856, 792, 694 cm^{-1}. HRMS (ESI−TOF): calcd for $[C_{21}H_{30}O_2+H]^+$ 315.2324, found 315.2321.

Butenolide 20c: Yield (171.2 mg, quant.); colorless oil; $[\alpha]_D^{25}$ = −138.3 (*c* = 0.35, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.8 Hz, 3H), 1.37−1.14 (m, 20H), 1.42–1.46 (m, 2H), 1.54–1.61 (m, 1H), 1.95–2.02 (m, 1H), 5.48–5.51 (m, 1H), 6.27 (d, *J* = 1.4 Hz, 1H), 7.44–7.49 (m, 5H) ppm. ^{13} NMR (125 MHz, $CDCl_3$): δ = 14.1, 22.7, 24.5, 29.2, 29.3, 29.4, 29.6, 29.61, 29.63, 31.9, 33.5, 82.3, 114.4, 127.0, 127.1, 129.2, 130.2, 131.2, 167.8, 172.9 ppm. IR

($CHCl_3$): ν_{max} = 2929, 1761, 1649, 1590, 1447, 1122, 1078, 1040, 946, 856, 709, 666 cm^{-1}. HRMS (ESI–TOF): calcd for $[C_{23}H_{34}O_2+Na]^+$ 365.2451, found 365.2448.

General procedure for the synthesis of 4-phenylbutyrolactones, (13a-c) and (14a-c): To a solution of **20a-c** (0.3 mmol) in absolute EtOH (5.0 mL) was added 10% Pd-C (3.0 mg, 10 mol%) and the reaction mixture stirred under H_2 (1 atm, balloon pressure) for 1 h at room temperature. The reaction mixture was then filtered through a small pad of celite and washed with EtOAc (3 × 5 mL). The filtrate was concentrated under *vacuo* to afford the diastereomeric mixture **13a-c/14a-c** (*anti:syn* = 1:1.2-2) in quantitative yield in each case. The diastereomeric mixture was separated by column chromatography using petroleum ether/EtOAc (19:1) as eluent to furnish pure *anti*-butyrolactones (**13a-c**) and *syn*-butyrolactones (**14a-c**).

Butyrolactone 13a: Yield (21 mg, 30%); colorless oil; $[\alpha]_D^{25}$ = 22.3 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 6.8 Hz, 3H), 1.21–1.34 (m, 5H), 1.48–1.52 (m, 1H), 1.65–1.70 (m, 2H), 2.71 (dd, *J* = 17.7, 10.5 Hz, 1H), 2.91 (dd, *J* = 17.6, 8.7 Hz, 1H), 3.26–3.33 (m, 1H), 4.42–4.47 (m, 1H), 7.23–7.39 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.4, 25.3, 31.5, 34.1, 37.6, 47.7, 87.1, 127.2, 127.7, 129.1, 139.1, 175.7 ppm. IR ($CHCl_3$): ν_{max} = 3019, 2927, 2855, 1779, 1423, 1264, 1044, 928, 778, 669 cm^{-1}. HRMS (ESI–TOF): calcd for $[C_{15}H_{20}O_2+Na]^+$ 255.1356, found 255.1352.

Butyrolactone 13b: Yield (42.8 mg, 45%); colorless oil; $[\alpha]_D^{25}$ = 18.2 (*c* = 0.45, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 6.0 Hz, 3H), 1.26–1.42 (m, 18H), 1.49–1.62 (m, 2H), 2.65 (dd, *J* = 17.2, 10.9 Hz, 1H), 2.85 (dd, *J* = 17.6, 8.7 Hz, 1H), 3.19 (dd, *J* = 17.5, 8.8 Hz, 1H), 4.36 (dd, *J* = 12.5, 6.0 Hz, 1H), 7.17–7.31 (m, 5H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 22.7, 25.6, 29.27, 29.3, 29.4, 29.5, 29.6, 31.9, 34.1, 37.6, 47.7, 87.1, 127.2, 127.7, 129.1, 139.1, 175.7 ppm. IR ($CHCl_3$): ν_{max} = 3018, 2927, 2855, 1777, 1541, 1445, 1236, 1119, 1043, 928, 775, 669 cm^{-1}. HRMS (ESI–TOF): calcd for $[C_{21}H_{32}O_2+Na]^+$ 339.2295, found 339.2295.

Butyrolactone 13c: Yield (46.5 mg, 45%); colorless oil; $[\alpha]_D^{25}$ = 19.8 (*c* = 0.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.8 Hz, 3H), 1.22–1.54 (m, 22H), 1.45–1.69 (m, 2H), 2.72 (dd, *J* = 17.7, 10.5 Hz, 1H), 2.92 (dd, *J* = 17.7, 8.8 Hz, 1H), 3.26 (dd, *J* = 18.9, 8.6 Hz, 1H), 4.42 (dd, *J* = 14.2, 6.2 Hz, 1H), 7.23–7.38 (m, 5H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 22.7, 25.7, 29.3, 29.34, 29.4, 29.5, 29.57, 29.6, 29.7, 31.9, 34.1, 37.6, 47.7, 87.1, 127.2, 127.7, 129.1, 139.1, 175.7 ppm. IR ($CHCl_3$): ν_{max} = 3019, 2927, 2854, 1771, 1555, 1442, 1222, 1043, 928, 876, 669 cm^{-1}. HRMS (ESI–TOF): calcd for $[C_{23}H_{36}O_2+Na]^+$ 367.2608, found 367.2608.

Butyrolactone 14a: Yield (41.8 mg, 60%), colorless oil; $[\alpha]_D^{25}$ = 28.1 (*c* = 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 7.0 Hz, 3H), 1.13–1.33 (m, 7H), 1.37–1.46 (m, 1H), 2.74 (dd, *J* = 17.4, 4.9 Hz, 1H), 2.93 (dd, *J* = 17.5, 8.5 Hz, 1H), 3.69–3.74 (m, 1H), 4.68–4.73 (m, 1H), 7.11–7.14 (m, 2H), 7.27–7.36 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.4, 25.5, 31.1, 31.4, 35.8, 44.6, 84.3, 127.6, 127.8, 128.8, 138.1, 176.9 ppm. IR ($CHCl_3$): ν_{max} = 3014, 2930, 2852, 1779, 1463, 1365, 1187, 1043, 1024, 920, 671 cm^{-1}. HRMS (ESI–TOF): calcd for $[C_{15}H_{20}O_2+Na]^+$ 255.1356, found 255.1354.

Butyrolactone 14b: Yield (42.7 mg, 45%); colorless oil; $[\alpha]_D^{25}$ = 24.2 (*c* = 0.35, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.0 Hz, 3H), 1.13–1.42 (m, 20H), 2.75 (dd, *J* = 17.5, 4.9 Hz, 1H), 2.94 (dd, *J* = 17.5, 8.6 Hz, 1H), 3.69–3.74 (m, 1H), 4.68–4.72 (m, 1H), 7.12–7.14 (m, 2H), 7.27–7.35 (m, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 22.7, 25.8, 29.2, 29.3, 29.33, 29.4, 29.5, 29.6, 31.1, 31.9, 35.8, 44.6, 84.3, 127.6, 127.8, 128.7, 138.1, 176.9 ppm. IR ($CHCl_3$): ν_{max} = 3014, 2926, 2857, 1779, 1466, 1362, 1187, 1043, 920, 674 cm^{-1}. HRMS (ESI–TOF): calcd for $[C_{21}H_{32}O_2+Na]^+$ 339.2295, found 339.2298.

Butyrolactone 14c: Yield (48.6 mg, 47%); colorless oil; $[\alpha]_D^{25}$ = 28.1 (*c* = 0.25, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.86 (t, *J* = 7.0 Hz, 3H), 1.12–1.45 (m, 24H), 2.74 (dd, *J* = 17.5, 4.9 Hz, 1H), 2.94 (dd, *J* = 17.5, 8.6 Hz, 1H), 3.70–3.74 (m, 1H), 4.68–4.72 (m, 1H), 7.12–7.26 (m, 2H), 7.29–7.34 (m, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 22.7, 25.8, 29.2, 29.3, 29.4, 29.5, 29.6, 29.64, 31.1, 31.9, 35.8, 44.6, 84.3, 127.6, 127.8, 128.7, 138.1, 176.9 ppm. IR ($CHCl_3$): ν_{max} = 3014, 2926, 2857, 1779, 1468, 1357, 1187, 1038, 1027, 669 cm^{-1}. HRMS (ESI–TOF): calcd for $[C_{23}H_{36}O_2+Na]^+$ 367.2608, found 367.2605.

General procedure for the synthesis of butyrolactones 11a-c and 12a under Sharpless oxidation conditions.[13] To a solution of **13a-c** or **14a** (0.1 mmol) in CCl_4 (1 mL), CH_3CN (1 mL) and H_2O (2 mL) were added sequentially $NaIO_4$ (321 mg, 1.5 mmol, 15 equiv) and $RuCl_3.3H_2O$ (1.44 mg, 0.0055 mmol, 5.5 mol%) under vigorous stirring. After 48 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and filtered through a pad of celite and washed with CH_2Cl_2 (3 × 5 mL). The filtrate was concentrated to afford virtually pure butyrolactones **11a-c** or **12a** respectively.

Carboxylic acid 11a: Yield (20 mg, quant.); white solid; m.p = 100–102 °C. $[\alpha]_D^{25}$ = 40.2 (*c* = 0.3, $CHCl_3$); lit.[7s] m.p = 105 °C, $[\alpha]_D^{25}$ = 53.7 (*c* = 1.82, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.6 Hz, 3H), 1.11–1.56 (m, 6H), 1.65–1.85 (m, 2H), 2.81 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.94 (dd, *J* = 18.0, 8.6 Hz, 1H), 3.05–3.15 (m, 1H), 4.57–4.65 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.4, 24.8, 31.3, 32.0, 35.3, 45.4, 81.9, 174.4, 176.0 ppm. IR ($CHCl_3$): ν_{max} = 3467, 3020, 2930, 2856, 1779, 1746, 1461, 1021, 910, 770, 669 cm^{-1} HRMS (ESI–TOF): calcd for $[C_{10}H_{16}O_4+H]^+$ 201.1127, found 201.1131.

Carboxylic acid 11b: Yield (28.4 mg, quant.); white solid; m.p = 116–118 °C. $[\alpha]_D^{25}$ = 44.0 (*c* = 0.2, $CHCl_3$), lit.[7n] $[\alpha]_D^{25}$ = 44.8 (*c* = 0.25, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3H), 1.10–1.60 (m, 18H), 1.65–1.85 (m, 2H), 2.82 (dd, *J* = 17.9, 9.8 Hz, 1H), 2.94 (dd, *J* = 17.9, 8.6 Hz, 1H), 3.06–3.13 (m, 1H), 4.58–4.65 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 22.7, 25.2, 29.2, 29.3, 29.4, 29.5, 29.6, 31.9, 35.4, 45.4, 81.8, 174.4, 175.9 ppm. IR ($CHCl_3$): ν_{max} = 3437, 3020, 2928, 2856, 1779, 1717, 1602, 1521, 1424, 1019, 929, 845, 669, 626 cm^{-1}. HRMS (ESI–TOF): calcd for $[C_{16}H_{28}O_4+H]^+$ 285.2066, found 285.2068.

Carboxylic acid 11c: Yield (31.2 mg, quant.); white solid; m.p = 104–106 °C. $[\alpha]_D^{25}$ = 38.8 (*c* = 0.35, $CHCl_3$), for enantiomer lit.[7s] $[\alpha]_D^{25}$ = −42.8 (*c* = 1.72, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3H), 1.10–1.60 (m, 22H), 1.65–1.85 (m, 2H), 2.82 (dd, *J* = 17.8, 8.4 Hz, 1H), 2.94 (dd, *J* = 17.8, 8.4 Hz, 1H), 3.06–3.13 (m, 1H), 4.58–4.65 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 22.7, 25.2, 29.2, 29.3, 29.4, 29.5, 29.6, 29.62, 29.7, 31.9, 32.0, 34.1, 35.4, 45.4, 81.9, 174.5, 175.6 ppm. IR ($CHCl_3$): ν_{max} = 3451, 3018, 2923, 1657, 1534, 1221, 1062, 894, 856, 809, 772, 686, 628, 541 cm^{-1}. HRMS (ESI–TOF): calcd for $[C_{18}H_{32}O_4+H]^+$ 313.2379, found 313.2376.

Carboxylic acid 12a: Yield (20 mg, quant.); white solid; m.p = 101–103 °C. $[\alpha]_D^{25}$ = 44.0 (*c* = 0.14, $CHCl_3$); lit.[7y] $[\alpha]_D^{29}$ = 54.08 (*c* = 0.51, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.1 Hz, 3H), 1.25–1.75 (m, 8H), 2.71 (dd, *J* = 17.7, 8.5 Hz, 1H), 2.90 (dd, *J* = 17.7, 5.1 Hz, 1H), 3.42–3.52 (m, 1H), 4.67 (dd, *J* = 13.7, 7.1 Hz,

View Article Online
DOI: 10.1039/C6OB02598C

1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.4, 25.5, 31.2, 31.3, 31.9, 44.1, 80.3, 174.9, 175.1 ppm. IR ($CHCl_3$): ν_{max} = 3645, 3019, 2926, 2855, 1770, 1469, 1443, 1161, 1040, 971, 928, 669 cm^{-1}. HRMS (ESI−TOF): calcd for $[C_{10}H_{16}O_4+H]^+$ 201.1127, found 201.1130.

General procedure for α-methylation of acids 11b, 11c or 12a to 1-3 respectively.[7n] To a solution of **11b**, **11c** or **12a** (0.10 mmol) in THF (4 mL) at −78 °C was added NaHMDS (0.22 mL, 0.22 mmol, 1.0 M solution in THF, 2.2 equiv) and stirred for 1.5 h. MeI (62 μL, 1.0 mmol, 10.0 equiv) was added and the reaction mixture stirred at −78 °C for 2 h and then allowed to warm to −20 °C. 2N HCl (1.0 mL) was added and the mixture extracted with EtOAc (5 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by silica gel flash column chromatography (petroleum ether/EtOAc, 1:1) as eluent to provide **1-3** respectively as white solids in quantitative yields.

(+)-Nephrosteranic acid (1): Yield (29.8 mg, quant.); white solid; m.p = 94−96 °C. $[\alpha]_D^{25}$ = 26.9 (*c* = 0.14, $CHCl_3$); lit.[7c] m.p = 96−98 °C, $[\alpha]_D^{27}$ = 27.2 (*c* = 1.45, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3H), 1.02−1.61 (m, 18H), 1.37 (d, *J* = 7.3 Hz, 3H), 1.62−1.83 (m, 2H), 2.72 (dd, *J* = 11.3, 9.5 Hz, 1H), 2.97−3.01 (m, 1H), 4.46–4.50 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 14.5, 22.7, 25.3, 29.2, 29.3, 29.4, 29.5, 29.6, 31.9, 34.9, 39.8, 53.8, 79.3, 175.1, 176.6 ppm. IR ($CHCl_3$): ν_{max} = 3356, 3020, 2928, 2855, 1773, 1716, 1464, 1022, 669 cm^{-1}. HRMS (ESI−TOF): calcd for $[C_{17}H_{30}O_4+H]^+$ 299.2222, found 299.2217.

(+)-Rocellaric acid (2): Yield (32.6 mg, quant.); white solid; m.p = 98−100 °C. $[\alpha]_D^{25}$ = 26.9 (*c* = 2.0, $CHCl_3$); lit.[7s] $[\alpha]_D^{25}$ = 23.6 (*c* = 1.60, $CHCl_3$), lit.[7c] $[\alpha]_D^{25}$ = 27 (*c* = 0.87, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.8 Hz, 3H), 1.03–1.64 (m, 22H), 1.36 (d, *J* = 7.0 Hz, 3H), 1.65–1.85 (m, 2H), 2.69 (dd, *J* = 11.3, 9.5 Hz, 1H), 2.95–3.02 (m, 1H), 4.43–4.50 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 14.5, 22.7, 25.3, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 34.9, 39.8, 53.8, 79.4, 174.5, 176.6 ppm. IR ($CHCl_3$): ν_{max} = 3434, 3019, 2923, 2857, 1778, 1748, 1602, 1456, 1127, 1017, 925, 769, 669 cm^{-1}. HRMS (ESI−TOF): calcd for $[C_{19}H_{34}O_4+H]^+$ 327.2535, found 327.2529.

(+)-Phaseolinic acid (3): Yield (21.4 mg, quant.); white solid; m.p = 137−139 °C. $[\alpha]_D^{25}$ = 115 (*c* = 0.2, $CHCl_3$), lit.[7i] $[\alpha]_D^{25}$ = 111.4 (*c* = 0.22, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.0 Hz, 3H), 1.21–1.57 (m, 6H), 1.33 (d, *J* = 7.1 Hz, 3H), 1.57–1.67 (m, 2H), 3.0–3.09 (m, 1H), 3.22 (dd, *J* = 9.6, 8.2, 1H), 4.69−4.73 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 14.4, 22.4, 25.3, 31.0, 31.3, 36.4, 51.6, 77.4, 174.8, 177.5 ppm. IR ($CHCl_3$): ν_{max} = 3021, 2959, 2930, 2861, 1775, 1717, 1524, 1459, 1420, 1382, 1017, 984, 669, 625 cm^{-1}. HRMS (ESI−TOF): calcd for $[C_{11}H_{18}O_4+H]^+$ 215.1283, found 215.1289.

General procedure for α-methylenation of acids 11a-c to 8-10 respectively.[16] Methoxy magnesium methylcarbonate (Stiles reagent, 1.9 mL, 3.80 mmol, 38.0 equiv., 2 M solution in DMF) was added under inert atmosphere to **11a-c** (0.1 mmol) and the solution stirred at 135 °C for 60 h. After cooling, the reaction mixture was acidified with dropwise addition of cold 10% HCl (7 mL) at 0 °C. Then CH_2Cl_2 (10 mL) was added to the mixture and stirred for 0.5 h. The aqueous layer was extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The crude compound was used directly for the next reaction.

The residue was treated with 1.5 mL of a freshly prepared stock solution [HOAc (4 mL), 37% formaldehyde in water (3 mL), *N*-methylaniline (1.0 mL) and NaOAc (0.12 g)] and stirred for 3 h at room temperature. Brine solution (10 mL containing 1 mL conc. HCl) was added and the aqueous layer extracted with Et_2O (5 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel flash column chromatography (CH_2Cl_2/EtOAc, 19:1) to provide **8-10** respectively in 60-64% yield.

(+)-Methylenolactocin (8): Yield (13.6 mg, 64%); white solid; m.p = 81−83 °C. $[\alpha]_D^{25}$ = 6.8 (*c* = 0.2, CH_3OH), lit.[7s] $[\alpha]_D^{25}$ = 2.25 (*c* = 1.46, CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.7 Hz, 3H), 1.11−1.58 (m, 6H), 1.65−1.81 (m, 2H), 3.62−3.64 (m, 1H), 4.78−4.83 (m, 1H), 6.02 (d, *J* = 2.8 Hz, 1H), 6.47 (d, *J* = 2.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.4, 24.4, 31.3, 35.7, 49.4, 78.8, 125.8, 132.4, 168.2, 173.8 ppm. IR ($CHCl_3$): ν_{max} = 3352, 3020, 2930, 1763, 1720, 1115, 1025, 929, 669 cm^{-1}. HRMS (ESI−TOF): calcd for $[C_{11}H_{16}O_4+H]^+$ 213.1127, found 213.1135.

(+)-Nephrosterinic acid (9): Yield (19 mg, 64%); white solid; m.p = 80−82 °C. $[\alpha]_D^{25}$ = 12.6 (*c* = 0.5, $CHCl_3$), lit. [7l] $[\alpha]_D^{32}$ = 13.0 (*c* = 0.66, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.8 Hz, 3H), 1.10–1.60 (m, 18H), 1.65–1.80 (m, 2H), 3.61−3.65 (m, 1H), 4.81−4.83 (m, 1H), 6.01 (d, *J* = 3.0 Hz, 1H,), 6.45 (d, *J* = 3.0 Hz, 1H), ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.7, 24.8, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 35.7, 49.4, 78.9, 125.6, 132.7, 168.2, 172.2 ppm. IR ($CHCl_3$): ν_{max} = 3684, 3020, 2957, 2928, 2856, 2433, 2400, 1763, 1719, 1602, 1523, 1475, 1423, 1117, 1018, 929, 850, 669, 626 cm^{-1}. HRMS (ESI−TOF): calcd for $[C_{17}H_{28}O_4+H]^+$ 297.2066, found 297.2072.

(+)-Protolichesterinic acid (10): Yield (19.5 mg, 60%); white solid; m.p. = 102−104 °C; $[\alpha]_D^{25}$ = 13.1 (*c* = 0.4, $CHCl_3$) lit.[7s] m.p. = 104−105 °C; $[\alpha]_D^{25}$ = 13.6 (*c* = 1.72, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.7 Hz, 3H), 1.10–1.60 (m, 22H), 1.65–1.80 (m, 2H), 3.61−3.63 (m, 1H), 4.80−4.84 (m, 1H), 6.01 (d, *J* = 2.8 Hz, 1H), 6.45 (d, *J* = 2.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.7, 24.8, 29.2, 29.3, 29.4, 29.5, 29.6, 31.9, 35.7, 49.6, 79.0, 132.7, 125.6, 168.3, 172.9 ppm. IR ($CHCl_3$): ν_{max} = 3682, 3020, 2927, 2855, 2400, 1759, 1714, 1602, 1516, 1466, 1109, 1024, 929, 669, 626 cm^{-1}. HRMS (ESI−TOF): calcd for $[C_{19}H_{32}O_4+H]^+$ 325.2379, found 325.2386.

Acknowledgements

We thank the Department of Science and Technology, New Delhi, (Grant No. SB/S1/OC-42/2013) and Board of Research in Nuclear Sciences (BRNS), Government of India (Basic Sciences, Grant No. 2013/37C/59/BRNS/2443) for financial support. J.L.N thanks Council of Scientific and Industrial Research (CSIR), New Delhi for research fellowship.

References

1 *(a)* Y. S. Rao, *Chem. Rev*., 1964, **64**, 353; *(b)* R. B. Gammill, C. A. Wilson and T. A. Bryson, *Synth. Commun*., 1975, **5**, 245; *(c)* H. M. R. Hoffmann and J. Rabe, *Angew. Chem. Int. Ed.,* 1985, **24**, 94; *(d)* S. S. C. Koch and A. R. Chamberlin, *J. Org. Chem.,* 1993, **58**, 2725 and references therein; *(e)* D. W. Knight, *Contemp. Org. Synth.,* 1994, **1**, 287; *(f)* R. R. A. Kitson, A. Millemaggi and R. J. K. Taylor, *Angew. Chem. Int. Ed*., 2009, **48**, 9426.

2 *(a)* J. Mulzer, N. Salimi and H. Hartl, *Tetrahedron: Asymmetry,* 1993, **4**, 457; *(b)* J. Mulzer, L. Kattner, A. R. Strecker, C. Schroder, J. Buschmann, C. Lehmann and P.

Luger, *J. Am. Chem. Soc.,* 1991, **113**, 4218; *(c)* P. A. Jacobi and P. Herradura, *Can. J. Chem*., 2001, **79**, 1727.

3 *(a)* W. Zopf, *Liebigs Ann. Chem.,* 1902, **324**, 39; *(b)* Y. Asahina and M. J. Asano, *Pharm. Soc. Jpn.,* 1927, **539**, 1; *Chem. Abstr*., 1928, **22**, 4470; *(c)* M. Asano and T. Kanematsu, *Chem. Ber.,* 1932, **65B**, 1175; *(d)* Y. Asahina and M. Yanagita, *Chem. Ber.,* 1936, **69B**, 120; *(e)* Y. Asahina and M. Yasue, *Chem. Ber.,* 1937, **70B**, 1053; *(f)* H. Gertig, *Diss. Pharm.,* 1963, **15**, 235; *Chem. Abstr.,* 1964, **60**, 2041; *(g)* L. G. J. Shah, *Ind. Chem. Soc.,* 1954, **31**, 253; *(h)* K. Aghoramurty, S. Neelakantan and T. R. J. Seshadri, *Sci. Ind. Res. (India)*, 1954, **13B**, 326; *Chem. Abstr.,* 1955, **49**, 8900; *(i)* S. Rangaswami and V. Subba Rao, *Ind. J. Pharm*., 1955, **17**, 50.

4 *(a*) D. Hoppe, *Angew. Chem. Int. Ed.,* 1984, **23**, 932; *(b)* H. Roder, G. Helmchen, E. M. Peters, K. Peters and H. G. V. Schnering, *Angew. Chem. Int. Ed., **1984***, **23**, 898; *(c)* A. Schlapbach and R. W. Hoffmann, *Eur. J. Org. Chem.,* 2001, 323.

5 *(a)* J. Bérdy, In Handbook of Antibiotic Compounds; CRS Press: Boca Raton, FL, 1982; Vol. IX; *(b)* S. Shibata, Y. Miura, H. Sugimura and Y. Toyoizumi, J. *Pharm. Soc. Jpn.,* 1948, **68**, 300; *Chem. Abstr.,* 1951, **45**, 6691; *(c)* C. J. Cavallito, D. McK. Freuhauf and J. H. Bailey, *J. Am. Chem. Soc.,* 1948, **70***,* 3724; *(d)* M. B. M. de Azevedo, M. M. Murta and A. E. Greene, *J. Org. Chem.,* 1992, **57**, 4567; *(e)* S. Drioli, F. Felluga, C. Forzato, P. Nitti and G. Pitacco, *Chem. Commun.,* 1996, 1289; *(f)* S. Huneck and K. Schreiber, *Phytochemistry,* 1972, **11**, 2429.

6 *(a)* T. Řezanka and I. A. Guschina, *Phytochemistry*, 2000, **54**, 635; *(b)* T. Řezanka and I. A. Guschina, *Phytochemistry*, 2001, **56**, 181; *(c)* A. Kondoh, A; Arlt, B. Gabor and A. Fürstner, *Chem*. *Eur. J.,* 2013, **19**, 7731.

7 *(a)* S. Shimada, Y. Hashimoto and K. Saigo, *J. Org. Chem.,* 1993, **58**, 5226; *(b)* M. M. Murta, de M. B. M. Azevedo and A. E. Greene, *J. Org. Chem.,* 1993, **58**, 7537; *(c)* H. Takahata, Y. Uchida and T. Momose, *J Org. Chem.,* 1995, **60**, 5628; *(d)* S. D. Mawson and R. T. Weavers, *Tetrahedron,* 1995, **51**, 11257; *(e)* T. Martin, C. M. Rodriguez, V. S. Martin, *J. Org. Chem.,* 1996, **61**, 6450; *(f)* Z. Zhang and X. Lu, *Tetrahedron: Asymmetry,* 1996, **7**, 1923; *(g)* R. N. Saicic and S. Z. Zard, *Chem. Commun.,* 1996, 1631; *(h)* M. P. Sibi and J. Ji, *Angew. Chem. Int. Ed.,* 1997**, 36,** 274; *(i)* S. Drioli, F. Felluga, C. Forzato, P. Nitti, G. Pitacco and E. Valentin, *J. Org. Chem.,* 1998**, 63***,* 2385; *(j)* Y. Masaki, H. Arasaki, A. Itoh, *Tetrahedron Lett*., 1999, **40**, 4829; *(k)* T.-P. Loh and P.-L. Lye, *Tetrahedron Lett.,* 2001, **42**, 3511; *(l)* P. Kongsaeree, P. Meepowpan and Y. Thebtaranonth, *Tetrahedron: Asymmetry,* 2001, **12**, 1913; *(m)* M. P. Sibi, P. Liu, J. Ji, S. Hajra and J.-X. Chen, *J. Org. Chem.,* 2002, **67**, 1738; *(n)* M. T. Barros, C. D. Maycock and M. R. Venture, *Org. Lett.,* 2003, **5**, 4097 and references therein; (o) M; Amador, X. Ariza, J; Garcia and J. Ortiz, *J. Org. Chem.,* 2004, **69**, 8172; *(p)* R. B. Chhor, B. Nosse, S. Sorgel, C. Bohm, M. Seitz and O. Reiser, *Chem. Eur. J.,* 2003, **9**, 260; *(q)* F. Schleth, T. Vogler, K. Harms and A. Studer, *Chem. Eur. J.,* 2004, **10**, 4171; (r) F. Schleth and A. Studer, *Angew. Chem. Int. Ed.,* 2004, **43**, 313; *(s)* S. Braukmuller and R. Brückner, *Eur. J. Org. Chem.* 2006, 2110; *(t)* G. P. Howell, S. P. Fletcher, K. Geurts, B. terHorst and B. L. Feringa, *J. Am. Chem. Soc.,* 2006, **128**, 14977; *(u)* N. Selvakumar, P. K; Kumar, K. C. S. Reddy and B. C. Chary, *Tetrahedron Lett*., 2007, **48**, 2021; *(v)* S. Bazin, L. Feray, N. Vanthuyne, D. Siri and M. P. Bertrand, *Tetrahedron,* 2007, **63**, 77; *(w)* D. Blanc, J. Madec, F. Popowyck, T. Ayad, P. Phansavath, V. Ratovelomanana-Vidal and J.-P. Genet, *Adv. Synth. Catal.* 2007, **349**, 943; *(x)* S. Hajra, A. Karmakar, A. K. Giri and S. Hazra, *Tetrahedron Lett.,* 2008, **49**, 3625; *(y)* M. Ghosh, S. Bose, S. Maity and S. Ghosh, *Tetrahedron Lett.,* 2009, **50**, 7102; *(z)* R. Jongkol R. Choommongkol, B. Tarnchompoo, P. Nimmanpipug and P. Meepowpan, *Tetrahedron,* 2009, **65**, 6382; *(aa)* S. Saha, S. C. Roy, *Tetrahedron,* 2010, **66**, 4278; *(ab)* A. K. Perepogu, D. Raman, U. S. N. Murty and V. J. Rao, *Synth. Commun.,* 2010, **40**, 686; *(ac)* B. Mao, K. Geurts, M. Fañanas-Mastral, A. W. van Zijl, S. P. Fletcher, A. J. Minnaard and B. L. Feringa, *Org. Lett.,* 2011, **13**, 948; *(ad)* J. Fournier, O. Lozano, C. Menozzi, S. Arseniyadis and J. Cossy, *Angew. Chem. Int. Ed.,* 2013**, 52**, 1257; *(ae)* H. Wang, P. Tang, Q. Zhou, D. Zhang, Z. Chen, H. Huang and Y. Qin, *J. Org. Chem.,* 2015*,* **80***,* 2494.

8 Formal synthesis of paraconic acids: *(a)* M. P. Sibi, K. P. Deshpande and A. J. L. Loggia, *Synlett,* **1996**, 343; *(b)* P. K. Mandal and S. C. Roy, *Tetrahedron,* 1999, **55***,* 11395; *(c)* X. Ariza, J. Garcia, M. López and L. Montserrat. *Synlett,* 2001, 120; *(d)* A. Brecht-Forster, J. Fitremann and P. Renaud, *Helv. Chim. Acta*., 2002, **85**, 3965; *(e)* Y.-S. Hon, C.-H; Hsieh and H.-F. Chen. *Synth. Commun.,* 2007, **37**, 1635; *(e)* C. B. Barreto Jr. and V. L. P. Pereira *Tetrahedron Lett*., 2009, **50**, 6389 and Ref. 8o.

9 *(a)* R. A. Fernandes and A. K. Chowdhury, *Eur. J. Org. Chem.,* 2011, 1106; *(b)* R. A. Fernandes and A. K. Chowdhury, *Tetrahedron: Asymmetry,* 2011, **22**, 1114; *(c)* R. A. Fernandes, M. B. Halle, A. K. Chowdhury and A. B. Ingle, *Tetrahedron: Asymmetry,* 2012, **23**, 60.

10 *(a)* R. A. Fernandes and A. B. Ingle, *Tetrahedron Lett*., 2009, **50**, 1122; *(b)* R. A. Fernandes and A. K. Chowdhury, *J. Org*. *Chem*., 2009, **74**, 8826; *(c)* R. A. Fernandes and A. B. Ingle, *Synlett,* 2010, 158; *(d)* R. A. Fernandes and P. Kattanguru, *J. Org*. *Chem*., 2012, **77**, 9357; *(e)* R. A. Fernandes and P. Kattanguru, *Asian J. Org*. *Chem*., 2013, **2**, 74; *(f)* R. A. Fernandes and V. P. Chavan, *Chem*. *Commun*., 2013, **49**, 3354; *(g)* R. A. Fernandes, P. H. Patil and A. K. Chowdhury, *Eur. J. Org. Chem.,* 2013, 237; *(h)* V. Bethi, P. Kattanguru and R. A. Fernandes, *Eur. J. Org. Chem.,* 2014, 3249; *(i)* R. A. Fernandes, P. H. Patil and A. K. Chowdhury, *Asian. J. Org. Chem.,* 2014, **3**, 58; *(j)* P. H. Patil and R. A. Fernandes, *RSC Adv*., 2015, **61**, 49189; *(k)* D. A. Chaudhari, P. Kattanguru and R. A. Fernandes, *RSC Adv.,* 2015, **5**, 42131; *(l)* D. A. Chaudhari, A. B. Ingle and R. A. Fernandes, *Tetrahedron: Asymmetry,* 2016, **27**, 114; *(m)* R. A. Kunkalkar, D. Laha and R. A. Fernandes, *Org. Biomol. Chem*., 2016, **14**, 9072.

11 *(a)* J. L. Nallasivam and R. A. Fernandes, *Eur. J. Org. Chem.,* 2015, 2012; *(b)* J. L. Nallasivam and R. Fernandes, A. *Eur. J. Org. Chem.,* 2015, 3558.

12 L. Vasamsetty, F. A. Khan and G. Mehta, *Tetrahedron,* 2015, **71**, 3209.

13 *(a)* P. H. J. Carlsen, T. Kabuki, V. S. Martin and K. B. Sharpless, *J. Org. Chem.,* 1981, **46**, 3936; *(b)* B. M. Trost, S. Vince and C. Yeh *Org. Lett.,* 2002, **4**, 3513; *(c)* R. A. Fernandes and J. L. Nallasivam, *Org. Biomol. Chem.,* 2012, ***10***, 7789; *(d)* J. S. Yadav, G. Rajendar, R. Srinivasa Rao and S. Pabbaraja, *J. Org. Chem.* 2013, **78**, 8524.

14 *(a)* M. M. Midland, D. C. McDowell, R. L. Hatch and A. Tramontano, *J. Am. Chem. Soc.,* 1980, **102**, 867; *(b)* M. M. Midland and K. Aleksander, *J. Org. Chem.,* 1982, **47**, 2814; *(c)* M. M. Midland, A. Tramontano, K. Aleksander, R. S. Graham, D. J. S. Tsai and D. B. Cardin, *Tetrahedron,* 1984, **40**, 1371.

15 The enantiomeric excess of the alkynols **16a-c** were determined by chiral HPLC method (see Supporting Information).

16 *(a)* H. L. Finkbeiner and M. Stiles, *J. Am. Chem. Soc.,* 1963, **85**, 616; *(b)* J. Martin, P. C. Watts and F. Johnson, *Chem. Commun.,* 1970, 27.