Organic & Biomolecular Chemistry

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 1280

Received 29th November 2012,
Accepted 4th January 2013

DOI: 10.1039/c3ob27321k

www.rsc.org/obc

Optically pure γ-butyrolactones and epoxy esters *via* two stereocentered HKR of 3-substituted epoxy esters: a formal synthesis of (−)-paroxetine, Ro 67-8867 and (+)-eldanolide†

Dattatray A. Devalankar, Pratibha U. Karabal and Arumugam Sudalai*

The HKR of racemic *anti*- or *syn*-3-substituted epoxy esters catalyzed by a Co(III)salen complex provides ready access to the corresponding enantioenriched 3,4-disubstituted γ-butyrolactones and 3-substituted epoxy esters. This strategy has been successfully employed in the formal synthesis of biologically active 3,4-disubstituted piperidine derivatives, (−)-paroxetine and Ro 67-8867 and a natural product, (+)-eldanolide.

Introduction

The γ-butyrolactone skeleton represents an important core structure in many biologically active natural products.[1] In particular, certain functionalized chiral γ-butyrolactones are sex attractant pheromones[2] such as eldanolide **1** and some are utilized as flavoring components.[3] In addition, they are also useful chiral synthons for accessing substituted piperidines, which are ubiquitous structural motifs present in numerous pharmaceuticals[4] such as paroxetine **3** and Ro 67-8867 **5** (Fig. 1). The enantiomerically pure epoxy esters **9** are also valuable 'building blocks' for the asymmetric synthesis of bioactive natural products.[5] Due to their interesting biological activity in medicinal chemistry, an efficient catalytic method for the synthesis of substituted γ-butyrolactones and epoxy esters from commercially available materials is of current interest.[6]

Recent methods in the synthesis of chiral 3,4-disubstituted γ-butyrolactones mainly include: (i) SmI_2-mediated reductive coupling of aldehydes with crotonates possessing 2-substituted 8-methoxy-1-naphthamides or *N*-methylephedrine as a chiral auxiliary;[7a,b] (ii) lipase PS-mediated resolution of substituted γ-butyrolactones[7c] and (iii) catalytic asymmetric cyclocarbonylation.[7d] On the other hand, the synthesis of chiral epoxy esters has generally been reported from chiral pool resources.[5]

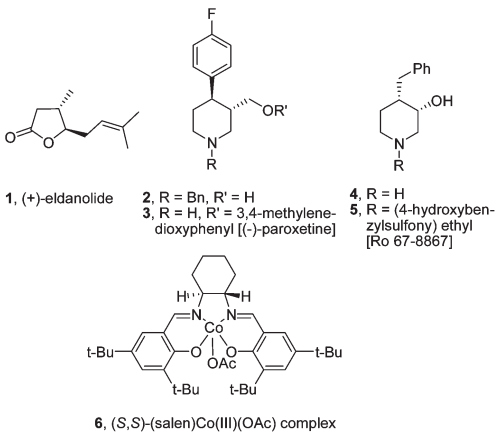


Fig. 1 Structure of biologically active γ-butyrolactone, substituted piperidines and Co(III)salen catalyst.

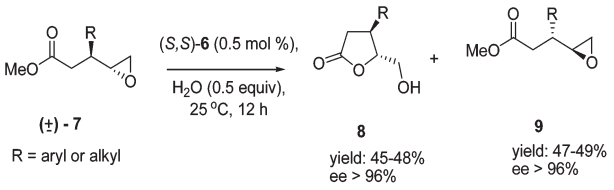
However, the reported methods suffer from certain limitations such as use of expensive catalysts, chiral pool resources, multiple steps or products obtained in low optical purity.

Jacobsen's hydrolytic kinetic resolution (HKR) with chiral cobalt catalysts has been comprehensively studied to obtain chiral epoxides and diols of high ees in excellent yields.[8] Despite impressive achievements, HKR has generally been applied to the resolution of simple terminal epoxides with one stereocentre.[9] Quite recently, we have reported an elegant protocol involving a two-stereocentered Co-catalyzed HKR of racemic terminal epoxides bearing adjacent C–O and C–N binding substituents to furnish enantiopure *syn* or *anti* alkoxy and azido epoxides and the corresponding 1,2-diols in high optical purity (up to 99% ee).[10] In the present work, it is of interest to extend its scope to include terminal epoxides bearing adjacent C–C binding substituents.

In this communication, we wish to report a flexible, novel single-step method that employs Co-catalyzed HKR of racemic 3-substituted (aryl or alkyl) epoxy esters **7** with two stereocentres to produce substituted γ-butyrolactones **8** and epoxy esters **9** in high optical purities (Scheme 1).

Chemical Engineering and Process Development Division, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411008, India.
E-mail: a.sudalai@ncl.res.in; Fax: +91-02025902676

†Electronic supplementary information (ESI) available: Experimental details and spectral data of all the new compounds. See DOI: 10.1039/c3ob27321k



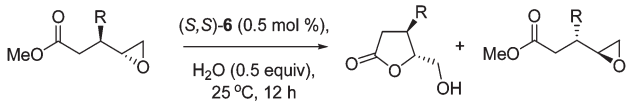
Scheme 1 Co-catalyzed HKR of racemic 3-substituted *anti* epoxy esters.

Results and discussion

Initially, when HKR of racemic *anti*-3-substituted epoxy ester **7a** was carried out with (*S*,*S*)-(salen)Co(OAc) complex **6** (0.5 mol%) and H_2O (0.5 equiv.), the corresponding *trans*-3,4-disubstituted γ-butyrolactone **8a** (45%) and 3-substituted epoxy ester **9a** (48%) were isolated in high yields and optical purity [**8a** (99% ee) and **9a** (97% ee)]. The formation of γ-butyrolactones can be explained on the basis of intramolecular cyclization of the chiral diol formed *in situ* with ester functionality. Encouraged by this result, we have examined its scope by subjecting several racemic *anti*-3-substituted epoxy esters **7a–h** to HKR, which proceeded smoothly, with complete regiocontrol, to give the respective enantioenriched *trans*-3,4-disubstituted γ-butyrolactones **8a–h** and *anti*-epoxy esters **9a–h** in excellent ees (96 to 99% ee) and high yields (45 to 49%). The results of such a study are shown in Table 1. The reaction thus exhibited generality with respect to the degree of functionalization of epoxides.

Similarly, when *syn*-3-substituted epoxy esters **10a–d** were subjected to HKR under identical reaction conditions, the corresponding chiral *cis*-3,4-disubstituted γ-butyrolactones **11a–d**

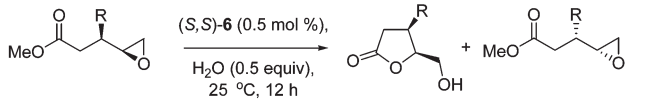
Table 1 Co-catalyzed HKR of racemic 3-substituted *anti*-epoxy esters



Entry	Substrates R (±) – **7(a–h)**	Lactones **8(a–h)** Yield[a] (%)	ee[b,c] (%)	Epoxides **9(a–h)** Yield[a] (%)	ee[b,c] (%)	s[d]
a	Phenyl	45	99	48	97	500
b	4-Fluorophenyl	46	99	49	99	535
c	4-Chlorophenyl	45	98	48	98	245
d	4-Bromophenyl	46	96	48	96	124
e	4-Methoxyphenyl	48	97	47	96	200
f	Methyl	46	97	48	96	170
g	Benzyl	47	99	48	97	581
h	3-Phenylpropyl	48	96	48	96	146

[a] Isolated yield after column chromatographic purification. [b] ee determined by chiral HPLC. [c] ee determined by Mosher's ester analysis for entries **8f** and **9f**. [d] The values for s (stereoselectivity factor) were calculated using the equation $s = \ln[1 - c(1 + ee)]/\ln[1 - c(1 - ee)]$, where c and ee are conversion and enantiomeric excess of the lactone.[11]

Table 2 Co-catalyzed HKR of racemic 3-substituted *syn*-epoxy esters

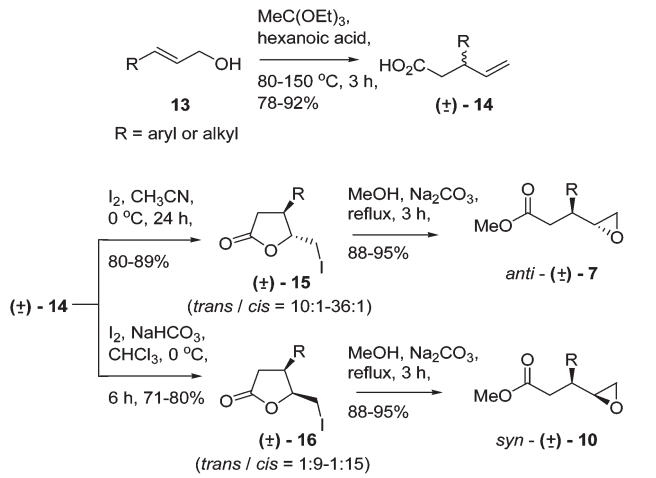


Entry	Substrates R (±) – **10(a–d)**	Lactones **11(a–d)** Yield[a] (%)	ee[b] (%)	Epoxides **12(a–d)** Yield[a] (%)	ee[b] (%)	s[c]
a	Phenyl	47	98	48	97	282
b	4-Fluorophenyl	46	98	48	98	261
c	4-Chlorophenyl	47	99	46	97	581
d	4-Bromophenyl	46	98	48	97	261

[a] Isolated yield after column chromatographic purification. [b] ee determined by chiral HPLC. [c] The values for s (stereoselectivity factor) were calculated using the equation $s = \ln[1 - c(1 + ee)]/\ln[1 - c(1 - ee)]$, where c and ee are conversion and enantiomeric excess of the lactone.[11]

and *syn*-epoxy esters **12a–d** were obtained in high yields and ees up to 99%. The results of this study are presented in Table 2.

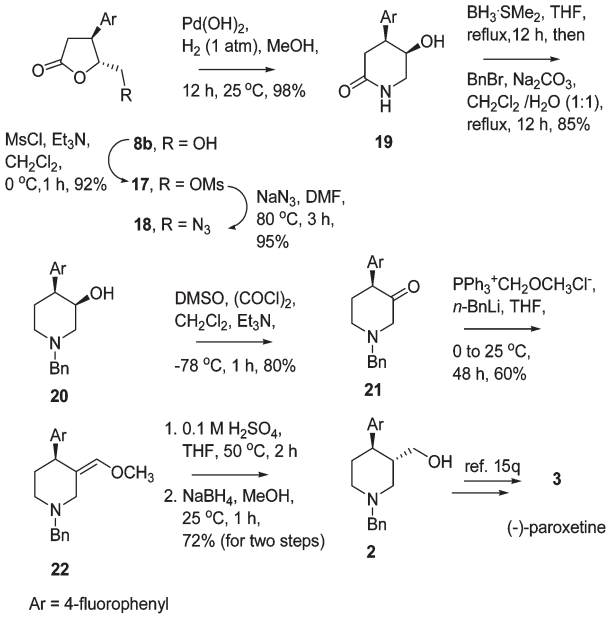
The racemic *anti*- and *syn*-3-substituted epoxy esters (7 and **10**), the substrates for HKR, were efficiently prepared in a highly diastereoselective manner from the corresponding allylic alcohols **13** by essentially following a three-step procedure:[12] (i) Johnson–Claisen rearrangement[13] of allylic alcohols **13** [$MeC(OEt)_3$, hexanoic acid (catalytic), 80–150 °C] gave acyclic olefinic acids **14**; (ii) diastereoselective iodolactonization of **14** gave *trans* or *cis* iodolactones (**15** or **16**) depending upon the reaction conditions employed (for *trans*: I_2, CH_3CN, 0 °C, 24 h; for *cis*: I_2, $NaHCO_3$, $CHCl_3$, 0 °C, 6 h); (iii) methanolysis of **15** or **16** under basic conditions produced the required racemic *anti*- or *syn*-3-substituted epoxy esters **7** or **10** (Scheme 2).



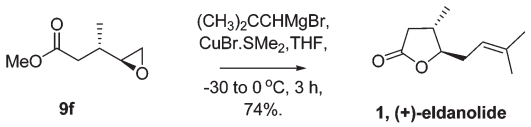
Scheme 2 Preparation of racemic 3-substituted *anti*/*syn* epoxy esters.

In this strategy, the relative stereochemistry is thus established prior to the HKR step itself and in this way a simple asymmetric reaction can be used to form enantiomerically pure substituted γ-butyrolactones and epoxy esters with two adjacent stereocentres.

Among the various applications of this two stereocentered HKR, an enantioselective synthesis of 3,4-disubstituted piperidines [*e.g.* (−)-paroxetine **3** and Ro 67-88675] and natural product (+)-eldanolide **1** attracted our attention due to their pharmaceutical importance. For example, (−)-paroxetine **3**, a *trans*-3,4-disubstituted piperidine derivative, is used in the treatment of depression, obsessive compulsive disorder and panic disorder[14] and its synthesis received considerable attention from synthetic chemists.[4c,15] Our synthesis of **3** commences from γ-butyrolactone **8b**. Mesylation of **8b** gave the mesylate **17** which was converted to the corresponding azide **18** (NaN_3, DMF, 80 °C) in 95% yield. Azide **18** was then subjected to intramolecular reductive cyclization over $Pd(OH)_2/H_2$ (1 atm) to afford *cis*-3,4-disubstituted piperidinone core **19** in 98% yield. Reduction of **19** with $BH_3{\cdot}SMe_2$ followed by *in situ* *N*-benzyl protection gave *cis*-piperidine derivative **20** in 85% yield. Swern oxidation of alcohol **20** gave ketone **21**, which on Wittig olefination with $Ph_3P{=}CHOMe$[15m] produced enol ether **22** in 60% yield. Acid hydrolysis of **22** followed by $NaBH_4$ reduction of the resulting aldehyde provided the known intermediate *N*-benzyl amino alcohol **2**,[15q] (overall yield 25% from **8b**) thus constituting a formal synthesis of (−)-paroxetine **3** (Scheme 3). Ro 67-8867 **5**, a high affinity, selective and activity-dependent antagonist of the *N*-methyl-D-aspartate (NMDA) receptor, has been reported to selectively block an NMDA receptor subtype in brain regions.[16] Its key intermediate **4**[17] was readily synthesized from an enantiomer of γ-butyrolactone **8g** (obtained from HKR of **7g** with (*R*,*R*)-Co salen as a catalyst)



Scheme 3 Formal synthesis of (−)-paroxetine.



Scheme 4 Synthesis of (+)-eldanolide.

by essentially following a similar sequence of reactions described in Scheme 3: (i) mesylation (MsCl, Et_3N, 0 °C); (ii) azidation (NaN_3, DMF, 80 °C); (iii) catalytic hydrogenation [$Pd(OH)_2$ (H_2, 1 atm)] and (iv) $BH_3{\cdot}SMe_2$-mediated reduction.

Finally, an elegant synthesis of natural product (+)-eldanolide **1**, a long range sex attractant isolated from the male wing gland of African sugarcane stem borer *Eldana sacharina*,[2,18] was achieved by the regioselective ring opening of chiral epoxide **9f** with $(Me)_2C{=}CHMgBr$ in a single step with an overall yield of 35% from **7f** (Scheme 4).

The absolute configuration of both chiral γ-butyrolactones **8** and **11** and epoxy esters **9** and **12** was ascertained by comparing optical rotations with those reported in the literature.[5d,7c,15q,17b,18e]

Conclusion

In conclusion, the (salen)Co(III)-catalyzed HKR of racemic *anti*- or *syn*-3-substituted epoxy esters provides a highly practical route to the synthesis of substituted enantioenriched γ-butyrolactones and 3-substituted epoxy esters, key intermediates in the synthesis of many bioactive molecules. This method has been successfully demonstrated in the efficient formal synthesis of (−)-paroxetine **3**, Ro 67-8867 **5** and (+)-eldanolide **1**. The reaction is convenient to carry out under mild conditions, displaying a wide range of substrate scope. We believe that this HKR strategy will find tremendous applications in the synthesis of bioactive molecules owing to the flexible nature of the synthesis of starting material and the ready availability of Co-catalysts in both enantiomeric forms.

Experimental section

A general experimental procedure for hydrolytic kinetic resolution (HKR) of 3-substituted epoxy esters (7a–h and 10a–d)

To a solution of (*R*,*R*)- or (*S*,*S*)-(salen)Co(II)complex (0.024 mmol, 0.5 mol%) in toluene (1 mL), acetic acid (0.014 g, 0.24 mmol) was added. It was allowed to stir at 25 °C in open air for 30 min during which time the color changed from orange-red to a dark brown and it was then concentrated under reduced pressure to get the Co(III)-salen complex-**6** as a brown colored solid. To this racemic 3-substituted epoxy esters **7**/**10** (4.85 mmol) and H_2O (0.043 g, 2.42 mmol) were added at 0 °C. The reaction was allowed to warm to 25 °C and stirred for 12 h. After completion of the reaction (monitored by TLC), the crude product was purified by column chromatography over silica gel to give chiral epoxy esters **9a–g** and **12a–d** [solvent

system; petroleum ether–ethyl acetate (9 : 1)] and chiral γ-butyrolactones **8a–g** and **11a–d** [solvent system; petroleum ether–ethyl acetate (1 : 1)] in pure form.

(4*S*, 5*R*)-5-(Hydroxymethyl)-4-phenyldihydrofuran-2(3*H*)-one (8a)

Yield: 45%, colorless solid; m.p.: 82 °C; $[\alpha]_D^{25}$ = −25.4 (*c* 1, $CHCl_3$); IR: ($CHCl_3$, cm^{-1}) 1778, 3443; ^1H NMR (200 MHz, $CDCl_3$) δ 2.04 (br s, 1H), 2.80 (dd, *J* = 9.9, 17.8 Hz, 1H), 3.10 (dd, *J* = 9.1, 17.8 Hz, 1H), 3.63–3.77 (m, 2H), 3.93–3.99 (m, 1H), 4.53 (m, 1H), 7.24–7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 37.23, 41.92, 61.73, 87.23, 127.19, 127.67, 129.12, 139.38, 176.30; HRMS (*m*/*z*): calculated $[M + H]^+$ for $C_{11}H_{13}O_3$: 193.0859; found: 193.0859; optical purity: 99% ee determined by HPLC analysis (Chiral OD-H column, *n*-hexane-2-propanol (50 : 50), 0.5 mL min^{-1}, 254 nm); retention time: t_{major} = 10.15 and t_{minor} = 11.35 min.

(*R*)-Methyl 3-((*S*)-oxiran-2-yl)-3-phenylpropanoate (9a)

Yield: 48%, colorless liquid; $[\alpha]_D^{25}$ = −12.7 (*c* 1, $CHCl_3$); IR: ($CHCl_3$, cm^{-1}) 1736; ^1H NMR (200 MHz, $CDCl_3$) δ 2.55 (dd, *J* = 2.6, 4.8 Hz, 1H), 2.72–3.12 (m, 5H), 3.60 (s, 3H), 7.20–7.34 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 37.37, 44.96, 46.95, 51.64, 55.29, 127.32, 127.67, 128.76, 139.89, 171.88; HRMS (*m*/*z*): calculated $[M + H]^+$ for $C_{12}H_{15}O_3$: 207.1016; found: 207.1014; optical purity: 97% ee determined by HPLC analysis (OD-H column, *n*-hexane–2-propanol (90 : 10), 0.5 mL min^{-1}, 254 nm); retention time: t_{minor} = 10.28 and t_{major} = 11.24 min.

(4*S*, 5*R*)-4-(4-Fluorophenyl)-5-(hydroxymethyl)dihydrofuran-2-(3*H*)-one (8b)

Yield: 46%, colorless solid; m.p.: 90 °C; $[\alpha]_D^{25}$ = −23.2 (*c* 1, $CHCl_3$); IR: ($CHCl_3$, cm^{-1}) 1777, 3439; ^1H NMR (200 MHz, $CDCl_3$) δ 2.21 (dd, *J* = 5.8, 7.3 Hz, 1H), 2.72 (dd, *J* = 9.7, 17.7 Hz, 1H), 3.03 (dd, *J* = 9.1, 17.7 Hz, 1H), 3.58–3.78 (m, 2H), 3.91–4.01 (m, 1H), 4.48 (m, 1H), 7.01–7.10 (m, 2H), 7.21–7.28 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 37.30, 41.22, 61.56, 87.21, 116.24 (d, *J* = 21.6 Hz), 128.89 (d, *J* = 8.1 Hz), 135.01 (d, *J* = 2.9 Hz), 162.10 (d, *J* = 246.6 Hz), 176.15; HRMS (*m*/*z*): calculated $[M + H]^+$ for $C_{11}H_{12}FO_3$: 211.0765; found: 211.0766; Optical purity: 99% ee determined by HPLC analysis (Chiral OJ-H column, *n*-hexane–2-propanol (50 : 50), 0.5 mL min^{-1}, 254 nm); retention time: t_{minor} = 10.72 and t_{major} = 11.28 min.

(4*S*, 5*S*)-5-(Hydroxymethyl)-4-phenyldihydrofuran-2(3*H*)-one (11a)

Yield: 47%, colorless thick liquid; $[\alpha]_D^{25}$ = −76.56 (*c* 1, $CHCl_3$); IR: ($CHCl_3$, cm^{-1}) 1780, 3440; ^1H NMR (200 MHz, $CDCl_3$) δ 2.30 (br s, 1H), 2.87 (dd, *J* = 8.9, 17.4 Hz, 1H), 3.04 (dd, *J* = 8.3, 17.4 Hz, 1H), 3.34–3.60 (m, 2H), 3.90 (q, *J* = 8.2 Hz, 1H), 4.79 (m, 1H), 7.22–7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 34.56, 43.16, 62.10, 86.37, 127.66, 127.84, 128.93, 136.46, 176.72; HRMS (*m*/*z*): calculated $[M + H]^+$ for $C_{11}H_{13}O_3$: 193.0859; found: 193.0859; optical purity: 98% ee determined by HPLC analysis (OJ-H column, *n*-hexane-2-propanol (50 : 50), 0.5 mL min^{-1}, 254 nm); retention time: t_{major} = 10.51 and t_{minor} = 13.84 min.

(*R*)-Methyl 3-((*R*)-oxiran-2-yl)-3-phenylpropanoate (12a)

Yield: 48%, colorless liquid; $[\alpha]_D^{25}$ = +17.3 (*c* 1, $CHCl_3$); IR: ($CHCl_3$, cm^{-1}) 1736; ^1H NMR (200 MHz, $CDCl_3$) δ 2.47 (dd, *J* = 2.6, 4.9 Hz, 1H), 2.58–2.83 (m, 3H), 3.14 (m, 1H), 3.26–3.36 (m, 1H), 3.63 (s, 3H), 7.20–7.32 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 36.50, 42.89, 45.67, 51.56, 54.43, 127.20, 127.87, 128.53, 139.46, 171.80; HRMS (*m*/*z*): calculated $[M + H]^+$ for $C_{12}H_{15}O_3$: 207.1016; found: 207.1028; optical purity: 97% ee determined by (OD-H column, *n*-hexane–2-propanol (90 : 10), 0.5 mL min^{-1}, 254 nm); retention time: t_{minor} = 13.68 and t_{major} = 14.93 min.

((2*R*, 3*S*)-3-(4-Fluorophenyl)-5-oxotetrahydrofuran-2-yl)methyl methanesulfonate (17)

Yield: 92%, colorless liquid; $[\alpha]_D^{25}$ = −31.9 (*c* 1, $CHCl_3$); IR: ($CHCl_3$, cm^{-1}) 1789; ^1H NMR (200 MHz, $CDCl_3$) δ 2.74 (dd, *J* = 9.7, 17.8 Hz, 1H), 3.05 (dd, *J* = 9.1, 18.1 Hz, 1H), 3.08 (s, 3H), 3.64 (q, *J* = 9.1 Hz, 1H), 4.27–4.49 (m, 2H), 4.61 (m, 1H), 7.04–7.13 (m, 2H), 7.22–7.29 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 36.75, 37.70, 41.89, 67.53, 82.94, 116.14 (d, *J* = 21.6 Hz), 128.93 (d, *J* = 8.1 Hz), 133.76 (d, *J* = 3.3 Hz), 162.36 (d, *J* = 248.1 Hz), 174.04; HRMS (*m*/*z*): calculated $[M + H]^+$ for $C_{12}H_{14}FO_5S$: 289.0540; found: 289.0536.

(4*S*, 5*R*)-5-(Azidomethyl)-4-(4-fluorophenyl)dihydrofuran-2-(3*H*)-one (18)

Yield: 95%, colorless liquid; $[\alpha]_D^{25}$ = −89.2 (*c* 1, $CHCl_3$); IR: ($CHCl_3$, cm^{-1}) 1789, 2105; ^1H NMR (200 MHz, $CDCl_3$) δ 2.71 (dd, *J* = 9.9, 17.8 Hz, 1H), 3.03 (dd, *J* = 8.9, 17.7 Hz, 1H), 3.26–3.71 (m, 3H), 4.51 (m, 1H), 7.02–7.11 (m, 2H), 7.18–7.26 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 36.91, 42.95, 51.86, 84.31, 116.52 (d, *J* = 21.6 Hz), 128.83 (d, *J* = 8.1 Hz), 134.02 (d, *J* = 3.3 Hz), 162.32 (d, *J* = 247.7 Hz), 174.08; HRMS (*m*/*z*): calculated $[M + H]^+$ for $C_{11}H_{11}FN_3O_2$: 236.0830; found: 236.0829.

(4*S*, 5*R*)-4-(4-Fluorophenyl)-5-hydroxypiperidin-2-one (19)

Yield: 98%, colorless solid; m.p.: 176 °C; $[\alpha]_D^{25}$ = +74.7 (*c* 1, MeOH); IR: ($CHCl_3$, cm^{-1}) 1636, 1652, 3439; ^1H NMR (200 MHz, MeOH-d_4) δ 2.33 (dd, *J* = 5.6, 17.3 Hz, 1H), 2.82 (dd, *J* = 12.2, 29.5 Hz, 1H), 3.11 (m, 1H), 3.25 (m, 1H), 3.48 (dd, *J* = 2.9, 13.0 Hz, 1H), 4.02 (m, 1H), 6.90–6.99 (m, 2H), 7.25–7.32 (m, 2H); ^{13}C NMR (50 MHz, $MeOD_4$): δ 33.46, 42.97, 50.19, 67.27, 115.93 (d, *J* = 21.6 Hz), 130.81 (d, *J* = 7.7 Hz), 138.64, 163.41 (d, *J* = 243.5 Hz), 174.57; HRMS (*m*/*z*): calculated $[M + H]^+$ for $C_{11}H_{13}FNO_2$: 210.0925; found: 210.0925.

(3*R*, 4*S*)-1-Benzyl-4-(4-fluorophenyl)piperidin-3-ol (20)

Yield: 85%, colorless solid; m.p.: 114 °C; $[\alpha]_D^{25}$ = +37.0 (*c* 1, $CHCl_3$); IR: ($CHCl_3$, cm^{-1}) 1509, 2936, 3446; ^1H NMR (200 MHz, $CDCl_3$) δ 1.66 (m, 1H), 2.15–2.36 (m, 2H), 2.35 (d, *J* = 11.3 Hz, 1H), 2.59 (d, *J* = 12.3 Hz, 1H), 3.06 (dd, *J* = 7.0, 30.4 Hz, 2H), 3.61 (s, 2H), 3.86 (s, 1H), 6.94–6.98 (m, 2H), 7.24–7.32 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.35, 45.80, 53.36,

60.20, 62.61, 68.94, 115.10 (d, J = 20.8 Hz), 127.52, 128.47, 129.17, 129.39 (d, J = 6.9 Hz), 137.28, 138.77, 161.59 (d, J = 243.5 Hz); Anal. Calcd for $C_{18}H_{20}FNO$ requires C, 75.76; H, 7.06; N, 4.91; found C, 75.78; H, 7.01; N, 4.82%.

(3*S*, 4*S*)-4-Benzylpiperidin-3-ol (4)

Yield: 80%, colorless solid; m.p.: 95.5 °C; $[\alpha]_D^{25}$ = −34.8 (c 1, $CHCl_3$) {lit.[17b] $[\alpha]_D^{20}$ −36.6 (c 1, $CHCl_3$)}; IR: ($CHCl_3$, cm^{-1}) 2923, 3441; ^1H NMR (200 MHz, MeOH-d_4) δ 1.29 (m, 1H), 1.64 (m, 2H), 2.27 (d, J = 13.43 Hz, 1H), 2.45 (m, 2H), 2.61 (dd, J = 7.02, 13.12 Hz, 1H), 2.94–3.01 (m, 2H), 3.53 (s, 1H), 7.05–7.10 (m, 3H), 7.13–7.16 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.60, 39.64, 42.10, 54.13, 60.53, 66.34, 127.14, 129.45, 130.34, 141.62; HRMS (m/z): calculated $[M + H]^+$ for $C_{12}H_{18}NO$: 192.1383; found: 192.1384.

(*S*)-1-Benzyl-4-(4-fluorophenyl)piperidin-3-one (21)

Yield: 80%, colorless liquid; $[\alpha]_D^{25}$ = +11.0 (c 1, $CHCl_3$); IR: ($CHCl_3$, cm^{-1}) 1722; ^1H NMR (200 MHz, $CDCl_3$) 2.14–2.25 (m, 2H), 2.51–2.64 (m, 1H), 2.89 (d, J = 13. 9 Hz, 1H), 3.03–3.10 (m, 1H), 3.37 (dd, J = 1.5, 13.9 Hz, 1H), 3.51 (t, J = 9.2 Hz, 1H), 3.63 (s, 2H), 6.97–7.14 (m, 4H), 7.31 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 32.74, 51.97, 54.36, 62.45, 64.46, 115.31 (d, J = 11.5 Hz), 127.52, 128.47, 129.17, 130.22 (d, J = 8.4 Hz), 133.67, 136.91, 161.79 (d, J = 247.4 Hz), 205.18; Anal. Calcd for $C_{18}H_{18}FNO$ requires C, 76.30; H, 6.40; N, 4.94; found C, 76.58; H, 6.32; N, 4.88%.

(*S*)-1-Benzyl-4-(4-fluorophenyl)-3-(methoxymethylene) piperidine (22)

Yield: 60%, colorless liquid; $[\alpha]_D^{25}$ = +7.0 (c 1, $CHCl_3$); IR: ($CHCl_3$, cm^{-1}) 1603, 1675, 2933; ^1H NMR (200 MHz, $CDCl_3$) 1.78 (m, 1H), 1.98 (m, 1H), 2.21 (m, 1H), 2.64 (d, J = 12.3 Hz, 1H), 2.90 (d, J = 11.6 Hz, 1H), 3.16 (d, J = 10.3 Hz, 1H), 3.42 (s, 3H), 3.50 (d, 13.0 Hz, 1H), 3.70 (d, J = 13.0 Hz, 1H), 3.83 (d, J = 12.3 Hz, 1H), 5.14 (s, 1H), 6.92 (m, 2H), 7.14–7.42 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 32.71, 43.90, 51.62, 52.88, 59.40, 63.01, 114.99 (d, J = 21.2 Hz), 117.53, 126.93, 128.14, 129.39, 129.82 (d, J = 7.6 Hz), 137.75, 137.93, 143.24, 161.88 (d, J = 246.6 Hz); Anal. Calcd for $C_{20}H_{22}FNO$ requires C, 77.14; H, 7.12; N, 4.50; found C, 77.24; H, 7.15; N, 4.41%.

((3*S*, 4*R*)-1-Benzyl-4-(4-fluorophenyl)piperidin-3-yl)-methanol (2)

Yield: 72%, colorless liquid; $[\alpha]_D^{25}$ = −15.2 (c 1, $CHCl_3$) {lit.[15q] $[\alpha]_D^{20}$ −16.0 (c 0.8, $CHCl_3$)}; IR: ($CHCl_3$, cm^{-1}) 3424; ^1H NMR (200 MHz, $CDCl_3$): δ 1.45–1.90 (m, 3H), 1.95–2.11 (m, 3H), 2.32 (m, 1H), 2.98 (m, 1H), 3.18–3.26 (m, 2H), 3.37 (dd, J = 2.5, 11.2 Hz, 1H), 3.54 (d, J = 13.2 Hz, 1H), 3.63 (d, J = 13.2 Hz, 1H), 6.98 (m, 2H), 7.17 (m, 2H), 7.34 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 29.77, 44.24, 44.36, 53.92, 57.36, 63.43, 64.34, 115.42 (d, J = 21.2 Hz), 127.14, 128.22, 128.86, 129.31, 138.15, 140.20 (d, J = 3.0 Hz), 161.59 (d, J = 245.0 Hz); Anal. Calcd for $C_{19}H_{22}FNO$ requires C, 76.22; H, 7.41; N, 4.68; found C, 76.23; H, 7.35; N, 4.61%.

(+)-Eldanolide (1)

Yield: 74%, colorless liquid; $[\alpha]_D^{25}$ = +48.5 (c 1, MeOH) {lit.[18e] $[\alpha]_D^{20}$ +48.2 (c 1.15, MeOH)}; IR: ($CHCl_3$, cm^{-1}) 1781; ^1H NMR (200 MHz, $CDCl_3$) 1.12 (d, J = 6.6 Hz, 3H), 1.64 (s, 3H), 1.73 (s, 3H), 2.10–2.42 (m, 4H), 2.66 (m, 1H), 4.07 (q, J = 6.2 Hz, 1H), 5.17 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.81, 18.02, 25.88, 32.20, 35.09, 37.05, 86.94, 118.02, 135.41, 176.18; Anal. Calcd for $C_{10}H_{16}O_2$ requires C, 71.39; H, 9.59; found C, 71.20; H, 9.42%.

Acknowledgements

DAD and PUK thanks CSIR, New Delhi for the award of a Senior Research Fellowship. The authors are also thankful to Dr V. V. Ranade, Chair, Chemical Engineering and Process Development Division for his constant encouragement and support.

References

1 (*a*) R. Bandichhor, B. Nosse and O. Reiser, *Top. Curr. Chem.*, 2005, **243**, 43; (*b*) R. R. A. Kitson, A. Millemaggi and R. J. K. Taylor, *Angew. Chem., Int. Ed.*, 2009, **48**, 9426.

2 (*a*) G. Kunesch, P. Zagatti, J. Y. Lallemand, A. Debal and J. P. Vigneron, *Tetrahedron Lett.*, 1981, **22**, 5271; (*b*) J. P. Vigneron, R. Meric, M. Larcheveque, A. Debal, J. Y. Lallemand, G. Kunesch, P. Zagatti and M. Gallois, *Tetrahedron*, 1984, **40**, 3521.

3 (*a*) M. Masuda and K. Nishimura, *Phytochemistry*, 1971, **10**, 1401; (*b*) Y. S. Rao, *Chem. Rev.*, 1976, **76**, 625; (*c*) Y. S. Rao, *Chem. Rev.*, 1964, **64**, 353.

4 (*a*) B. E. Stephens and F. Liu, *J. Org. Chem.*, 2009, **74**, 254; (*b*) M. Venkataiah, G. Reddipalli, L. S. Jasti and N. W. Fadnavis, *Tetrahedron: Asymmetry*, 2011, **22**, 1855; (*c*) C. D. Risi, G. Fanton, G. P. Pollini, C. Trapella, F. Valente and V. Zanirato, *Tetrahedron: Asymmetry*, 2008, **19**, 131; (*d*) S. W. Pelletier, in *Alkaloids: Chemical and Biological Perspectives*, Wiley, New York, 1985, vol. 3; (*e*) M. G. P. Buffat, *Tetrahedron*, 2004, **60**, 1701.

5 (*a*) H.-J. Ha and Y.-G. Yim, *Synth. Commun.*, 2000, **30**, 581; (*b*) D. B. Collum, J. H. McDonald and W. C. Still, *J. Am. Chem. Soc.*, 1980, **102**, 2118; (*c*) P. A. Bartlett and J. Myerson, *J. Am. Chem. Soc.*, 1978, **100**, 3950; (*d*) J. S. Yadav and P. S. R. Reddy, *Synthesis*, 2007, 1070; (*e*) P. A. Bartlett and J. Myerson, *J. Org. Chem.*, 1979, **44**, 1625; (*f*) K. Mori and T. Umemura, *Tetrahedron Lett.*, 1982, **23**, 3391.

6 (*a*) P. Y. Toullec, E. Genin, S. Antoniotti, J.-P. Genet and V. Michelet, *Synlett*, 2008, 707; (*b*) E. Genin, P. Y. Toullec, S. Antoniotti, C. Brancour, J.-P. Genet and V. Michelet, *J. Am. Chem. Soc.*, 2006, **128**, 3112; (*c*) D. A. Evans, M. C. Kozlowski, J. A. Murry, C. S. Burgey, K. R. Campos, B. T. Connell and R. J. Staples, *J. Am. Chem. Soc.*, 1999, **121**, 669; (*d*) M. Seitz and O. Reiser, *Curr. Opin. Chem. Biol.*,

2005, **9**, 285; (*e*) L. Ferrie, D. Bouyssi and G. Balme, *Org. Lett.*, 2005, **7**, 3143; (*f*) Z.-H. Peng and K. A. Woerpel, *Org. Lett.*, 2001, **3**, 675; (*g*) T. Okada, K. Sakaguchi, T. Shinada and Y. Ohfune, *Tetrahedron Lett.*, 2011, **52**, 5740; (*h*) B. Mao, Y. Ji, M. Fananas-Mastral, G. Caroli, A. Meetsma and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2012, **51**, 3168; (*i*) M. P. Sibi, P. Liu, J. Ji, S. Hajra and J.-X. Chen, *J. Org. Chem.*, 2002, **67**, 1738 and references cited therein.

7 (*a*) Y. Zhang, Y. Wang and W.-M. Dai, *J. Org. Chem.*, 2006, **71**, 2445; (*b*) S.-i. Fukuzawa, K. Seki, M. Tatsuzawa and K. Mutoh, *J. Am. Chem. Soc.*, 1997, **119**, 1482; (*c*) H.-J. Ha, K.-N. Yoon, S.-Y. Lee, Y.-S. Park, M.-S. Lim and Y.-G. Yim, *J. Org. Chem.*, 1998, **63**, 8062; (*d*) S. K. Mandal, S. R. Amin and W. E. Crowe, *J. Am. Chem. Soc.*, 2001, **123**, 6457.

8 M. Tokunaga, J. F. Larrow, F. Kakiuchi and E. N. Jacobsen, *Science*, 1997, **277**, 936.

9 For one stereocentre resolution using HKR (*a*) P. Kumar, V. Naidu and P. Gupta, *Tetrahedron*, 2007, **63**, 2745; (*b*) P. Kumar and P. Gupta, *Synlett*, 2009, 1367; (*c*) Q. Yu, Y. Wu, L.-J. Xia, M.-H. Tang and Y.-L. Wu, *Chem. Commun.*, 1999, 129; (*d*) P. Kumar, P. Gupta and S. V. Naidu, *Chem.–Eur. J.*, 2006, **12**, 1397; (*e*) S. A. Burova and F. E. McDonald, *J. Am. Chem. Soc.*, 2004, **126**, 2495; (*f*) P. Kumar and S. V. Naidu, *J. Org. Chem.*, 2006, **71**, 3935.

10 For two stereocentre resolution using HKR in one step (*a*) R. S. Reddy, P. V. Chouthaiwale, G. Suryavanshi, V. B. Chavan and A. Sudalai, *Chem. Commun.*, 2010, **46**, 5012; (*b*) D. A. Devalankar and A. Sudalai, *Tetrahedron Lett.*, 2012, **53**, 3213; (*c*) Y.-J. Kim and J. Tae, *Synlett*, 2006, 61.

11 (*a*) S. H. Eliel, S. H. Wilen and L. N. Mander, in *Stereochemistry of Organic Compounds*, Wiley-Interscience, New York, 1994, pp. 395–415; (*b*) H. B. Kagan and J. C. Fiaud, in *Topics in Stereochemistry*, vol. 14, pp. 249–330.

12 (*a*) F. B. Gonzalez and P. A. Bartlett, *Org. Synth.*, 1986, **64**, 175; (*b*) A. R. Chamberlin, M. Dezube and P. Dussault, *Tetrahedron Lett.*, 1981, **22**, 4611.

13 W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T.-t. Li, D. J. Faulkner and M. R. Peterson, *J. Am. Chem. Soc.*, 1970, **92**, 741.

14 N. S. Gunasekara, S. Noble and P. Benfield, *Drugs*, 1988, **55**, 85.

15 (*a*) K. Sugi, N. Itaya, T. Katsura, M. Igi, S. Yamazaki, T. Ishibashi, T. Yamaoka, Y. Kawada, Y. Tagami, M. Otsuki and T. Ohshima, *Chem. Pharm. Bull.*, 2000, **48**, 529; (*b*) M. Amat, J. Hidalgo and J. Bosch, *Tetrahedron: Asymmetry*, 1996, **7**, 1591; (*c*) M. Amat, J. Bosch, J. Hidalgo, M. Canto, M. Perez, N. Llor, E. Molins, C. Miravitlles, M. Orozco and J. Luque, *J. Org. Chem.*, 2000, **65**, 3074; (*d*) L. T. Liu, P.-C. Hong, H.-L. Huang, S.-F. Chen, C.-L. J. Wang and Y.-S. Wen, *Tetrahedron: Asymmetry*, 2001, **12**, 419; (*e*) K. S. K. Murthy, A. W. Rey and M. Tjepkema, *Tetrahedron Lett.*, 2003, **44**, 5355; (*f*) S. Yamada and I. Jahan, *Tetrahedron Lett.*, 2005, **46**, 8673; (*g*) T. A. Johnson, M. D. Curtis and P. Beak, *J. Am. Chem. Soc.*, 2001, **123**, 1004; (*h*) T. A. Johnson, D. O. Jang, B. W. Slafer, M. D. Curtis and P. Beak, *J. Am. Chem. Soc.*, 2002, **124**, 11689; (*i*) D. A. Greenhalgh and N. S. Simpkins, *Synlett*, 2002, 2074; (*j*) J. Cossy, O. Mirguet, D. G. Pardo and J.-R. Desmurs, *Eur. J. Org. Chem.*, 2002, 3543; (*k*) T. Senda, M. Ogasawara and T. Hayashi, *J. Org. Chem.*, 2001, **66**, 6852; (*l*) G. Hughes, M. Kimura and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 11253; (*m*) P. K. Koech and M. J. Krische, *Tetrahedron*, 2006, **62**, 10594; (*n*) A. S. Paraskar and A. Sudalai, *Tetrahedron*, 2006, **62**, 4907; (*o*) M. Ito, A. Sakaguchi, C. Kobayashi and T. Ikariya, *J. Am. Chem. Soc.*, 2007, **129**, 290; (*p*) T. Nemoto, T. Sakamoto, T. Fukuyama and Y. Hamada, *Tetrahedron Lett.*, 2007, **48**, 4977; (*q*) J. F. Bower, T. Riis-Johannessen, P. Szeto, A. J. Whitehead and T. Gallagher, *Chem. Commun.*, 2007, 728; (*r*) S. Brandau, A. Landa, J. Franzen, M. Marigo and K. A. Jorgensen, *Angew. Chem., Int. Ed.*, 2006, **45**, 4305; (*s*) P. S. Hynes, P. A. Stupple and D. J. Dixon, *Org. Lett.*, 2008, **10**, 1389; (*t*) G. Valero, J. Schimer, I. Cisarova, J. Vesely, A. Moyano and R. Rios, *Tetrahedron Lett.*, 2009, **50**, 1943; (*u*) M. S. Yu, I. Lantos, Z.-Q. Peng, J. Yu and T. Cacchio, *Tetrahedron Lett.*, 2000, **41**, 5647; (*v*) M-h. Kim, Y. Park, B.-S. Jeong, H.-g. Park and S.-s. Jew, *Org. Lett.*, 2010, **12**, 2826; (*w*) K. Takasu, N. Nishida, A. Tomimura and M. Ihara, *J. Org. Chem.*, 2005, **70**, 3957 and references cited therein.

16 (*a*) M. Grauert, W. D. Bechtel, H. A. Ensinger, H. Merz and A. J. Carter, *J. Med. Chem.*, 1997, **40**, 2922; (*b*) A. P. Guzikowski, E. R. Whittemore, R. M. Woodward, E. Weber and J. F. W. Keana, *J. Med. Chem.*, 1997, **40**, 2424.

17 (*a*) M. Scalone and P. Waldmeier, *Org. Process Res. Dev.*, 2003, **7**, 418; (*b*) I. Dechamps, D. G. Pardo, P. Karoyan and J. Cossy, *Synlett*, 2005, 1170.

18 (*a*) F. Villar, T. Kolly-Kovac, O. Equey and P. Renaud, *Chem.–Eur. J.*, 2003, **9**, 1566; (*b*) F. Villar, O. Equey and P. Renaud, *Org. Lett.*, 2000, **2**, 1061; (*c*) H. Paulsen and D. Hoppe, *Tetrahedron*, 1992, **48**, 5667; (*d*) Y. Suzuki, W. Mori, H. Ishizone, K. Naito and T. Honda, *Tetrahedron Lett.*, 1992, **33**, 4931; (*e*) L. Kong, Z. Zhuang, Q. Chen, H. Deng, Z. Tang, X. Jia, Y. Li and H. Zhai, *Tetrahedron: Asymmetry*, 2007, **18**, 451.