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**PAPER**

# CN-assisted oxidative cyclization of cyano cinnamates and styrene derivatives: a facile entry to 3-substituted chiral phthalides†

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The asymmetric dihydroxylation (AD) of *o*-cyano cinnamates and styrene derivatives leads to efficient construction of chiral phthalide frameworks in high optical purities. This unique reaction is characterized by unusual synergism between CN and osmate groups resulting in rate enhancement of the AD process. The method is amply demonstrated by the synthesis and the structural/stereochemical assignment of the natural products.

## Introduction

Chiral phthalides [isobenzofuran-1(3*H*)-ones] comprising of 5-membered lactones are found in a large number of plant products displaying broad and potent biological activities.[1] Due to the biological importance of 3-substituted phthalides **1–3** (Fig. 1), their molecular architectures have become a platform for new synthetic methodology development.[2] Over the past two decades, newer methods toward introducing C-3 chirality in phthalides have been established, which include (i) hydrogenation of ketones (Noyori *et al.*),[3a] (ii) addition of zinc reagent to aldehydes (Butsugan *et al.*),[3b] (iii) asymmetric tandem process (Lin *et al.*),[3c] (iv) transesterification followed by cycloaddition (Tanaka and Yamamoto groups),[3d,e] (v) alkynylation of aldehydes (Trost *et al.*),[3f] (vi) cyclization approach (Cheng *et al.*),[3g] (vii) organocatalytic aldol-lactonization process (Wang *et al.*),[3h] and reductive cyclization of 2-acylarylcarboxylates (Xu and Lin *et al.*).[3i] Unfortunately, many such processes employ either expensive organometallic reagents in stoichiometric amounts,[3b,f,g] or chiral auxiliaries[4] and they often lack broad substrate scope and higher reaction stereoselectivity; only a few are atom economical.[5]

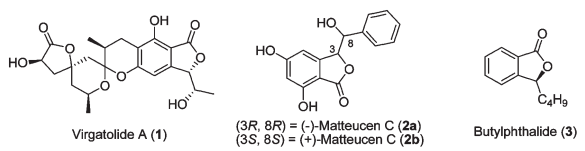


**Fig. 1** Structures of naturally occurring 3-substituted phthalides **1–3**.

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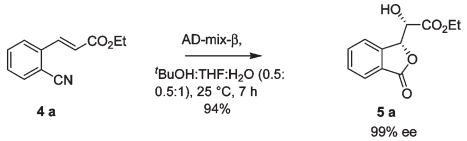
The Sharpless' asymmetric dihydroxylation (AD) of alkenes has emerged as a most reliable method for the preparation of chiral 1,2-diols, widely found in bioactive compounds and pharmaceuticals. Ligand acceleration is central to the efficiency and selectivity of the AD catalytic process.[6]

## Results and discussion

Herein, we report a single-step oxidative cyclization of cyanocinnamates and styrene derivatives to afford 3-substituted phthalides in high yields *via* synergetic acceleration of CN and osmate ester groups present in proximity positions.

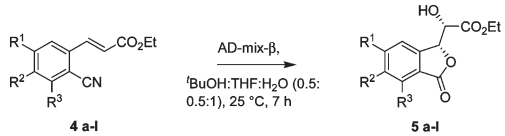
We have recently reported a novel protocol of AD process and Co-catalyzed "one-pot" reductive cyclization ($CoCl_2$–$NaBH_4$) of *nitro* cyclic sulfites that led to the construction of 3-substituted tetrahydroquinolin-3-ols.[7] In analogy with this, we reasoned that subjecting *cyano* cyclic sulfites to the same reaction conditions should afford synthetically useful benzazepines.[8] To our surprise, when ethyl 2-cyanocinnamate **4a** was subjected to a typical AD-mix-β process for 7 h, with THF as co-solvent for better solubility, the corresponding chiral phthalide **5a** was obtained exclusively in 99% ee (Scheme 1).

This unexpected transformation is characterized by high rate, excellent yield and enantioselectivity which is attributed to coordination assistance provided by the neighboring CN group to the osmate ester, leading to faster hydrolysis of the osmate ester in the catalytic cycle. Incidentally, the rate of AD process for electron-deficient *o*-substituted cinnamates is generally




**Scheme 1** Os-catalyzed oxidative cyclization of cyano cinnamates.

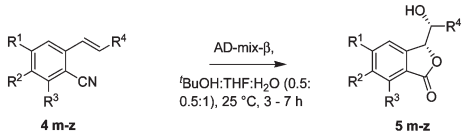
**Table 1** CN-assisted Os-catalyzed oxidative cyclization of cyano ethyl cinnamates




| Entry | $R^1$ | $R^2$ | $R^3$ | Yield[a] (%) | ee[b,c] (%) |
|---|---|---|---|---|---|
| a | H | H | H | 94 | 99 |
| b | OMe | H | H | 95 | 99 |
| c | OMe | OMe | H | 94 | 99 |
| d | H | OMe | OMe | 94 | 99 |
| e | OMe | H | OMe | 94 | 99 |
| f | OMe | OMe | OMe | 92 | 99 |
| g | OTs | OMe | H | 93 | 99 |
| h | OBn | OMe | H | 94 | 99 |
| i | F | H | H | 94 | 99 |
| j | $NO_2$ | H | H | 93 | 99 |
| k | –O–$CH_2$–O– | | H | 95 | 98 |
| l | (*E*)-Ethyl 3-(1-cyanonaphthalen-2-yl) acrylate | | | 94 | 98 |

[a] Isolated yield after column chromatographic purification. [b] ee determined by chiral HPLC analysis (see the ESI†). [c] ee determined by Mosher's ester analysis for entries h, i & l.

**Table 2** CN-assisted Os-catalyzed oxidative cyclization of cyano styrene derivatives




| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield[a] (%) | ee[b,c,d] (%) |
|---|---|---|---|---|---|---|
| m | H | H | H | H | 95 | 99 |
| n | OMe | H | H | H | 95 | 99 |
| o | OMe | OMe | H | H | 93 | 99 |
| p | H | OMe | OMe | H | 94 | 99 |
| q | OMe | H | OMe | H | 94 | 99 |
| r | OMe | OMe | OMe | H | 92 | 99 |
| s | OTs | OMe | H | H | 93 | 99 |
| t | OBn | OMe | H | H | 94 | 99 |
| u | F | H | H | H | 94 | 99 |
| v | –O–$CH_2$–O– | | H | H | 93 | 99 |
| w | H | H | H | $C_3H_7$ | 93 | 97 |
| x | OMe | OMe | H | $CH_2OTBS$ | 94 | 97 |
| y | OMe | OMe | H | Ph | 94 | 97 |
| z | OMe | OMe | H | n-$C_6H_{13}$ | 92 | 98 |

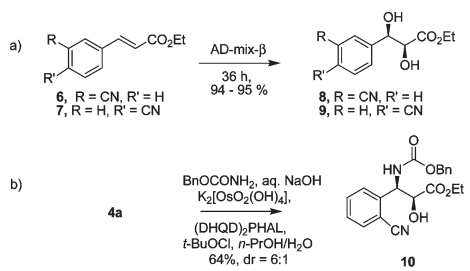
[a] Isolated yield after column chromatographic purification. [b] ee determined by chiral HPLC analysis (see the ESI†). [c] ee determined by Mosher's ester analysis for entries t, u, w–z. [d] Reaction completed in 3 h for entries m–v.

reported to be sluggish (48 h to 7 days) giving products invariably with moderate enantioselectivity (88% ee).[9]

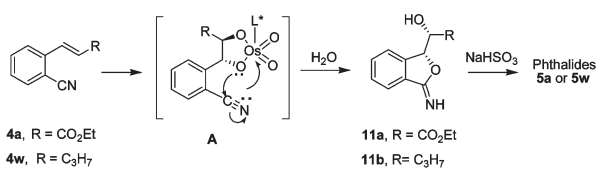
Encouraged by this result, we examined the scope of the reaction with other cyano cinnamate esters **4a-l** (Table 1). In every case, the reaction proceeded rapidly in 7 h giving the desired phthalides **5a-l** in excellent yields and enantioselectivities (up to 99%). For instance, substrates having halogen (entry i), highly electron-rich (entry f) or electron-deficient (entry j) substituents on the aromatic ring including 2-naphthyl nuclear system (entry l) underwent this oxidative cyclization smoothly affording the corresponding phthalides **5a-l** in excellent yields.

Subsequently, we extended our study to include other styrene derivatives bearing different functionalities on the aromatic nucleus as well as on the β-position of the styrene derivative side chain ($R^4$) (Table 2). It was again found that this oxidative cyclization AD process displayed a wide substrate scope tolerating alkyl, aryl, alkoxy, fluoro or tosyl groups. Excellent yields (93–95%) and enantioselectivities (97–99% ee) were indeed realized in all cases. The stereochemistry of the cyclized products was assigned according to the previously established absolute configuration of phthalides as well as in accordance with AD rules.[10]

In order to account for the course of the reaction, the following experiments (Scheme 2) were conducted: (i) AD-mix-β of substrates **6** & **7** for 36 h gave the corresponding cyanodiols **8** & **9** respectively, indicating that both CN and C=C groups must be positioned in proximity for CN coordination assistance to take place; (ii) asymmetric aminohydroxylation[11] of **4a** gave the expected amino alcohol **10** (64%) with no phthalide formation, suggesting that coordination of CN onto imino osmate ester is thermodynamically less favorable, due to its reduced Lewis acid character;[12] (iii) in addition, imino intermediates **11a-b** were indeed isolated in 20% yield during the AD-mix-β of substrates




**Scheme 2** Investigation on the mechanistic detail of oxidative cyclization.




**Scheme 3** Mechanism of CN-assisted Os-catalyzed oxidative cyclization.

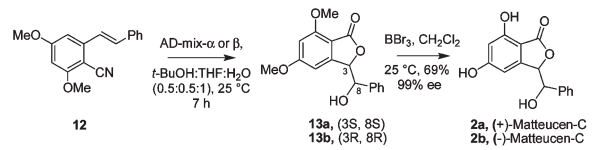
**4a** and **4w**. This study clearly excludes the hydrolysis of CN to $CO_2H$ followed by cyclization route, (iv) addition of benzonitrile as an external source of CN-assistance resulted in no rate enhancement for the AD process. On the basis of these results, a mechanistic model is shown in species **A** with a synergism involving co-ordination of CN to Os(VI) and concurrent attack of osmate ester onto electropositive carbon of CN is shown that probably helps to accelerate the hydrolysis of osmate ester. This results in 5-*exo-dig* type cyclization[13] to afford iminoesters **11a-b**, which finally lead to the formation of phthalides **5a** or **5w** (Scheme 3).

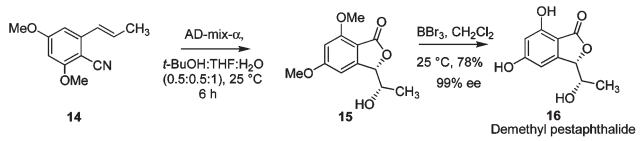
**Table 3** Competitive experiments[a]

| Entry | Substrates | Product | Yield[b,c] % |
|---|---|---|---|
| 1 | **4a** + ethyl cinnamate | **5a** | 92 |
| 2 | **12** + 3,5 dimethoxy stilbene | **13** | 93 |
| 3 | **4m** + styrene | **5m** | 94 |
| 4 | **4o** + 3,5 dimethoxy styrene | **5o** | 92 |
| 5 | **4r** + 3,4,5 trimethoxy styrene | **5r** | 92 |

[a] Reagents and conditions: 1 : 1 Molar equivalents of aromatics substrates with and without cyano substitution (1 mmol each), AD-mix-β (0.5 mol%), *t*BuOH–THF–$H_2O$ (0.5 : 0.5 : 1), 25 °C, 3 h for entries 3–5 and 7 h for entries 1 and 2. [b] Isolated yields. [c] 5–8% of 1,2-diol from the corresponding substrates without cyano substitution was indeed isolated.




**Scheme 4** Concise synthesis of (+) and (−)-matteucen C (**2a-b**).




**Scheme 5** Short synthesis of demethyl pestaphthalide (**16**).

The higher reactivity of cyano substituted cinnamates and styrenes were substantiated by carrying out several competitive experiments involving 1 : 1 molar equivalents of aromatic substrates with and without cyano substitution; the results of which are presented in Table 3. The results clearly show that cyano substituted substrates react almost 10–12 times faster than the one without cyano substitution, giving excellent yields of phthalides.

This protocol has subsequently been demonstrated in the asymmetric synthesis of three natural products: (i) demethyl pestaphthalide **16**, an intermediate in the biosynthesis of virgatolide A (**1**),[2a] which shows cytotoxic activity against HeLa cells; (ii) matteucen C (**2a-b**),[2b] a Chinese medicinal herb used in the treatment of hemostatics and relieving ostalgia; (iii) 3-butylphthalide (**3**), an anticonvulsant drug for the treatment of stroke[2c,f] (Fig. 1). The reported routes to synthesise these natural products obviously have several limitations.[14] This methodology has thus established a concise synthesis of **3**, **2a-b** and **16** in high optical purities starting from **5w**, **12** and **14** respectively in 2 steps of AD of alkenes followed by demethylation with $BBr_3$ or deoxygenation using Barton–McCombie protocol[15] (Schemes 4 and 5). Interestingly, the first asymmetric synthesis of two stereoisomers of matteucen C (**2a-b**) has unambiguously established the stereochemical *syn* relationship of C-3 and C-8 positions.

## Conclusion

We have demonstrated a novel CN-assisted oxidative cyclization for the synthesis of a wide variety of 3-substituted phthalides and their structural analogues *via* AD process of cyano cinnamates and styrene derivatives. This reaction is highly practical in the sense that the products were obtained in excellent yields and optical purities (97–99% ee) and shows broad substrate scope and good functional group tolerance. The synergism shown by CN and osmate groups in proximity helps to enhance the rate of this reaction. The synthetic potential of this protocol is further illustrated with a concise "one-pot" synthesis of three natural products in high optical purities. We believe that this oxidative intramolecular cyclization AD strategy should find wide applications in the total synthesis of other bioactive phthalide frameworks.

## Experimental

### Typical procedure

A 50 mL RB flask was charged with $K_3Fe(CN)_6$ (0.988 g, 3 mmol), $K_2CO_3$ (0.414 g, 3 mmol), *tert*-BuOH (2.5 mL), THF (2.5 mL) and $H_2O$ (5 mL) and stirred for 10 min. Subsequently, $(DHQD)_2PHAL$ (0.008 g, 1 mol%) and $K_2OsO_4{\cdot}2H_2O$ (0.002 g, 0.5 mol%) were added and the stirring continued for additional 30 min. To this reaction mixture, *o*-cyano alkene (1 mmol) was added and allowed to stir for 7 h at 25 °C. After completion of reaction (as monitored by TLC), sodium bisulphite (1 g) was added slowly at 0 °C. The organic layer was separated, aqueous layer extracted with ethyl acetate (3 × 10 ml) and the combined organic layers washed with brine (15 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure to yield the crude product. Flash column chromatographic purification [silica gel (230–400 mesh) and petroleum ether–EtOAc as an eluent] gave **5a-z** in pure form with high yields and ee.

**(*S*)-Ethyl-2-((*R*)-1,3-dihydro-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (5a).** Yield: 94%; colorless solid; mp 146–148 °C; 99% ee by chiral HPLC analysis (Chiracel OJ-H, *n*-hexane–iPrOH, 90 : 10, 0.5 mL $min^{-1}$) retention time 12.16 (99.65%) and 13.80 (0.35%); $[\alpha]_{25}^{D}$ −95.65 (*c* 1.24, $CHCl_3$); IR ($CHCl_3$): 762, 856, 968, 1027, 1068, 1078, 1210, 1298, 1349, 1467, 1611, 1652, 1720, 1768, 2924, 3014, 3440 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.29 (t, $J$ = 7.17 Hz, 3H), 3.16 (d, $J$ = 5.79 Hz, 1H), 4.30 (q, $J$ = 7.17 Hz, 2H), 4.66 (dd, $J$ = 2.12, 5.81 Hz, 1H), 5.79 (d, $J$ = 2.12 Hz, 1H), 7.57 (t, $J$ = 7.06 Hz, 2H), 7.68–7.75 (m, 1H), 7.90–7.93 (m, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 13.8, 62.4, 70.3, 80.4, 122.0, 125.3, 126.4, 129.3, 134.0, 145.7, 169.82, 170.7; HRMS (ESI) calcd for $C_{12}H_{12}O_5$ $[M + H]^+$ 237.0763, found 237.0772.

**(*S*)-Ethyl-2-((*R*)-1,3-dihydro-5-methoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (5b).** Yield: 95%; colorless solid; mp 121–122 °C; 99% ee by chiral HPLC analysis (Chiracel OJ-H, *n*-hexane–iPrOH, 90 : 10, 1 mL $min^{-1}$) retention time 25.80 (99.55%) and 30.33 (0.45%); $[\alpha]_{25}^{D}$ −94.49 (*c* 1.15, $CHCl_3$); IR ($CHCl_3$): 724, 876, 1031, 1084, 1191, 1212, 1278, 1295, 1357, 1398, 1445, 1486, 1578, 1607, 1721, 1765, 2984, 3023, 3415 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.29 (t, $J$ = 7.20 Hz, 3H), 3.14 (brs, 3H), 3.91 (s, 3H), 4.29 (q, $J$ = 7.20 Hz, 2H), 4.63 (d, $J$ = 1.74, 1H), 5.69 (d, $J$ = 2.29 Hz, 1H), 6.96 (d, $J$ = 2.11 Hz, 1H), 7.05 (dd, $J$ = 2.11, 8.66 Hz, 1H), 7.80 (d, $J$ = 8.66 Hz, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 14.0, 55.8, 62.7, 70.5, 79.6, 106.0,

117.0, 118.9, 127.1, 148.5, 164.8, 169.5, 170.9; HRMS (ESI) calcd for $C_{13}H_{14}O_6$ $[M + H]^+$ 267.0869, found 267.0863.

**(*S*)-Ethyl-2-((*R*)-1,3-dihydro-5,6-dimethoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (5c).** Yield: 94%; colorless solid; mp 144–146 °C; 99% ee by chiral HPLC analysis (Chiracel OJ-H, *n*-hexane–iPrOH, 90 : 10, 0.5 mL $min^{-1}$) retention time 23.18 (99.36%) and 27.60 (0.64%); $[\alpha]_{25}^{D}$ −95.12 (*c* 1.12, $CHCl_3$); IR ($CHCl_3$): 758, 945, 1125, 1297, 1507, 1722, 1764, 2925, 3010, 3341 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.30 (t, $J$ = 7.20 Hz, 3H), 3.20 (d, $J$ = 6.23 Hz, 1H), 3.94 (s, 3H), 3.98 (s, 3H), 4.29 (q, $J$ = 7.25 Hz, 2H), 4.62 (dd, $J$ = 2.42, 6.16 Hz, 1H), 5.66 (d, $J$ = 2.20 Hz, 1H), 6.93 (s, 1H), 7.27 (s, 1H); $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 14.4, 56.2, 56.4, 61.2, 70.2, 81.2, 105.2, 105.8, 118.2, 141.7, 150.5, 154.8, 170.2, 171.3; HRMS (ESI) calcd for $C_{14}H_{16}O_7$ $[M + H]^+$ 297.0974, found 297.0979.

**(*S*)-Ethyl-2-((*R*)-1,3-dihydro-6,7-dimethoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (5d).** Yield: 94%, colorless solid; mp 110–112 °C; 99% ee by chiral HPLC analysis (Chiracel OJ-H, *n*-hexane–iPrOH, 90 : 10, 0.5 mL $min^{-1}$) retention time 23.90 (99.44%) and 27.87 (0.56%); $[\alpha]_{25}^{D}$ −95.28 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 762, 946, 1132, 1298, 1518, 1728, 1764, 2985, 3034, 3425 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.30 (t, $J$ = 7.19 Hz, 3H), 3.19 (brs, 1H), 3.91 (s, 3H), 4.10 (s, 3H), 4.29 (q, $J$ = 7.19 Hz, 2H), 4.57 (s, 1H), 5.65 (d, $J$ = 2.09 Hz, 1H), 7.13 (d, $J$ = 8.11 Hz, 1H), 7.23 (d, $J$ = 8.11 Hz, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 14.1, 56.7, 62.2, 62.6, 70.7, 79.0, 116.4, 118.8, 119.3, 138.5, 148.4, 152.9, 167.2, 170.9; HRMS (ESI) calcd for $C_{14}H_{16}O_7$ $[M + H]^+$ 297.0974, found 297.0979.

**(*S*)-Ethyl-2-((*R*)-1,3-dihydro-5,7-dimethoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (5e).** Yield: 94%, colorless solid; mp 154–156 °C; 99% ee by chiral HPLC analysis (Chiracel OJ-H, *n*-hexane–iPrOH, 90 : 10, 0.5 mL $min^{-1}$) retention time 18.37 (99.60%) and 21.74 (0.40%); $[\alpha]_{25}^{D}$ −96.29 (*c* 1.15, $CHCl_3$); IR ($CHCl_3$): 746, 985, 1130, 1287, 1514, 1723, 1762, 2954, 3085, 3414 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.32 (t, $J$ = 7.22 Hz, 3H), 3.37 (brs, 1H), 3.91 (s, 3H), 3.94 (s, 3H), 4.30 (q, $J$ = 7.22 Hz, 2H), 4.61 (s, 1H), 5.67 (s, 1H), 6.47 (s, 1H), 6.59 (s, 1H); $^{13}C$ NMR ($CD_3OD$): $\delta$ 14.6, 56.5, 56.9, 63.0, 71.9, 82.1, 99.9, 100.3, 108.1, 153.1, 160.9, 168.9, 170.6, 172.5; HRMS (ESI) calcd for $C_{14}H_{16}O_7$ $[M + H]^+$ 297.0974, found 297.0979.

**(*S*)-Ethyl-2-((*R*)-1,3-dihydro-5,6,7-trimethoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (5f).** Yield: 92%, colorless solid; mp 111–112 °C; $[\alpha]_{25}^{D}$ −94.65 (*c* 1.23, $CHCl_3$); IR ($CHCl_3$): 1012, 1094, 1140, 1254, 1350, 1475, 1602, 1765, 2954, 3085, 3408 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.31 (t, $J$ = 7.20 Hz, 3H), 3.09 (s,1H), 3.86 (s, 3H), 3.96 (s, 3H), 4.13 (s, 3H), 4.31 (q, $J$ = 7.20 Hz, 2H), 4.58 (d, $J$ = 2.16 Hz, 1H), 5.58 (d, $J$ = 2.16 Hz, 1H), 6.70 (s, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 13.9, 56.3, 61.1, 62.0, 62.4, 79.1, 99.6, 111.0, 142.0, 143.5, 152.1, 159.7, 167.3, 176.8; HRMS (ESI) calcd for $C_{15}H_{18}O_8$ $[M + H]^+$ 327.1080, found 327.1072.

**(*S*)-Ethyl-2-((*R*)-5-(*p*-toluenesulfonoyloxy)-1,3-dihydro-6-methoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (5g).** Yield: 93%, colorless solid; mp 107–108 °C; $[\alpha]_{25}^{D}$ −94.89 (*c* 1.15, $CHCl_3$); IR ($CHCl_3$): 768, 819, 1025, 1050, 1120, 1180, 1190, 1330, 1374, 1494, 1614, 1767, 2924, 3012, 3371 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.27 (t, $J$ = 7.20 Hz, 3H), 2.48 (s, 3H), 3.07 (s, 1H), 3.78 (s, 3H), 4.26 (q, $J$ = 7.20 Hz, 2H), 4.63 (d, $J$ = 2.16 Hz, 1H), 5.67 (d, $J$ = 2.16 Hz, 1H), 6.99 (s, 1H), 7.35 (d, $J$ = 8.14 Hz, 2H), 7.49 (s, 1H), 7.76 (d, $J$ = 8.14 Hz, 2H); $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 14.5, 21.8, 56.7, 61.4, 70.3, 71.6, 81.4, 107.4, 118.7, 119.7, 128.6, 130.1, 132.6, 139.5, 145.9, 147.9, 157.0, 168.8, 170.9; HRMS (ESI) calcd for $C_{20}H_{20}O_9S$ $[M + H]^+$ 437.0906, found 437.0912.

**(*S*)-Ethyl-2-((*R*)-5-(benzyloxy)-1,3-dihydro-6-methoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (5h).** Yield: 94%, colorless solid; mp 138–140 °C; $[\alpha]_{25}^{D}$ −96.04 (*c* 1.21, $CHCl_3$); IR ($CHCl_3$): 738, 856, 1025, 1078, 1130, 1184, 1195, 1336, 1395, 1494, 1645, 1765, 2942, 3035, 3413 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.28 (t, $J$ = 7.05 Hz, 3H), 3.04 (d, $J$ = 5.93 Hz, 1H), 3.94 (s, 3H), 4.27 (q, $J$ = 7.05 Hz, 2H), 4.55 (dd, $J$ = 2.59, 5.93 Hz, 1H), 5.22 (d, $J$ = 3.59 Hz, 2H), 5.61 (d, $J$ = 2.08 Hz, 1H), 6.94 (s, 1H), 7.26 (s,1H), 7.29–7.45 (m, 5H); $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 13.7, 55.7, 61.5, 70.3, 70.6, 79.9, 105.2, 105.8, 118.5, 127.0, 127.8, 128.3, 135.3, 139.9, 150.8, 153.6, 169.7, 170.4; HRMS (ESI) calcd for $C_{20}H_{20}O_7$ $[M + H]^+$ 373.1287, found 373.1293.

**(*S*)-Ethyl-2-((*R*)-5-fluoro-1,3-dihydro-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (5i).** Yield: 94%, colorless solid; mp 108–109 °C; $[\alpha]_{25}^{D}$ −95.41 (*c* 1.15, $CHCl_3$); IR ($CHCl_3$): 756, 891, 1052, 1097, 1130, 1190, 1325, 1374, 1485, 1629, 1765, 2928, 3015, 3351 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.30 (t, $J$ = 7.27 Hz, 3H), 3.17 (d, $J$ = 6.74 Hz, 1H), 4.31 (q, $J$ = 7.27 Hz, 2H), 4.62 (dd, $J$ = 2.25, 5.84 Hz, 1H), 5.74 (d, $J$ = 7.25 Hz, 1H), 7.23 (d, $J$ = 8.4 Hz, 2H), 7.91 ((dd, $J$ = 5.84, 8.39 Hz, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 13.9, 62.2, 70.3, 79.8, 109.6 (d, $J$ = 24.64 Hz), 117.7 (d, $J$ = 24.64 Hz), 122.7, 127.7, 148.6 (d, $J$ = 10.33 Hz), 166.4 (d, $J$ = 256.30 Hz), 168.6, 170.5; HRMS (ESI) calcd for $C_{12}H_{11}FO_5$ $[M + H]^+$ 255.0669, found 255.0660.

**(*S*)-Ethyl-2-((*R*)-1,3-dihydro-5-nitro-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (5j).** Yield: 93%, colorless solid; mp 146–148 °C; $[\alpha]_{25}^{D}$ −95.28 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 738, 829, 967, 1037, 1106, 1346, 1540, 1740, 1779, 2853, 2918, 3009, 3444 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 1.35 (t, $J$ = 7.20 Hz, 3H), 3.21 (d, $J$ = 6.15 Hz, 1H), 4.36 (q, $J$ = 7.20 Hz, 2H), 4.71 (d, $J$ = 3.60 Hz, 1H), 5.90 (s, 1H), 8.09 (d, $J$ = 8.24 Hz, 1H), 8.42–8.46 (m, 2H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 14.1, 63.3, 70.2, 80.2, 117.9, 125.3, 127.0, 131.8, 146.9, 151.7, 167.3, 170.2; HRMS (ESI) calcd for $C_{12}H_{11}NO_7$ $[M + H]^+$ 282.0614, found 282.0612.

**(*S*)-Ethyl-2-((*R*)-5-1,3-dihydro-5,6-dioxomethyl-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (5k).** Yield: 95%, colorless solid; mp 150–153 °C; $[\alpha]_{25}^{D}$ −95.74 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 786, 891, 1015, 1054, 1122, 1183, 1196, 1356, 1395, 1489, 1618, 1755, 2942, 3021, 3410 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.31 (t, $J$ = 7.14 Hz, 3H), 3.10 (brs, 1H), 4.30 (qd, $J$ = 1.40, 7.14 Hz, 2H), 4.56 (s, 1H), 5.62 (d, $J$ = 2.19 Hz, 1H), 6.14 (dd, $J$ = 1.40, 4.44 Hz, 2H), 6.89 (s, 1H), 7.20 (s, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 14.0, 62.6, 70.4, 79.6, 101.9, 102.7, 104.3, 120.4, 142.2, 149.6, 153.7, 169.3, 170.8; Analysis: $C_{13}H_{12}O_7$ requires C 55.72, H 4.32 found C 55.65, H 4.29%.

**(*S*)-Ethyl 2-((*R*)-1,3-dihydro-1-oxonaphtho[2,1-c]furan-3-yl)-2-hydroxyacetate (5l).** Yield: 94%, colorless solid; mp 107–109 °C; $[\alpha]_{25}^{D}$ −95.69 (*c* 1.15, $CHCl_3$); IR ($CHCl_3$): 784, 865, 989, 1010, 1106, 1210, 1275, 1291, 1319, 1368, 1573, 1607, 1750, 2978, 3084, 3457 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.28 (t, $J$ = 7.45 Hz, 3H), 3.14 (d, $J$ = 6.06 Hz, 1H), 4.31 (q, $J$ = 7.45 Hz, 2H), 4.74 (dd, $J$ = 2.14, 6.06 Hz, 1H), 5.85 (d, $J$ = 2.14 Hz, 1H), 7.58 (d, $J$ = 8.50 Hz, 1H), 7.63–7.78 (m, 2H), 7.97 (d, $J$ = 8.5 Hz, 1H), 8.16 (d, $J$ = 8.5 Hz, 1H) 8.97 (d, $J$ = 8.5 Hz, 1H); $^{13}C$ NMR ($CDCl_3$ + $CD_3OD$): $\delta$ 13.2, 61.5, 69.8, 80.3, 118.2, 118.6, 120.3, 122.4, 126.8, 128.0, 128.4, 133.0, 135.2, 147.6, 170.4; Analysis: $C_{16}H_{14}O_5$ requires C 67.13, H 4.93 found C 67.11, H 4.89%.

**(*R*)-3-(Hydroxymethyl)isobenzofuran-1(3*H*)-one (5m).** Yield: 95%, colorless solid; mp 101–104 °C; 99% ee by chiral HPLC analysis (Chiracel OJ-H, *n*-hexane–iPrOH, 90 : 10, 0.5 mL $min^{-1}$) retention time 8.03 (99.36%) and 9.24 (0.64%); $[\alpha]_{25}^{D}$ −78.12 (*c* 1.23, $CHCl_3$); IR ($CHCl_3$): 744, 847, 968, 1025, 1067, 1089, 1211, 1288, 1349, 1467, 1607, 1640, 1756, 2924, 3012, 3440 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): 2.61 (s, 1H), 3.90 (d, $J$ = 11.80 Hz, 1H), 4.14 (d, $J$ = 11.80 Hz, 1H), 5.54–5.59 (m, 1H), 7.55 (t, $J$ = 7.79 Hz, 2H), 7.70 (td, $J$ = 1.14, 7.42 Hz, 1H), 7.89 (d, $J$ = 7.42 Hz, 1H); $^{13}C$ NMR ($CDCl_3$ + $CD_3OD$): $\delta$ 61.7, 81.6, 121.6, 124.2, 125.6, 128.4, 133.4, 146.8, 170.6; HRMS (ESI) calcd for $C_9H_8O_3$ $[M + H]^+$ 165.0552, found 165.0559.

**(*R*)-3-(Hydroxymethyl)-5-methoxyisobenzofuran-1(3*H*)-one (5n).** Yield: 95%, colorless solid; mp 137–140 °C; 99% ee by chiral HPLC analysis (Chiracel OJ-H, *n*-hexane–iPrOH, 90 : 10, 1 mL $min^{-1}$) retention time 27.19 (99.36%) and 39.72 (0.64%); $[\alpha]_{25}^{D}$ −78.36 (*c* 1.12, $CHCl_3$); IR ($CHCl_3$): 728, 868, 1026, 1256, 1490, 1607, 1640, 1749, 2853, 2923, 3440 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): 2.31 (brs, 1H), 3.84–3.91 (m, 4H), 4.06–4.14 (m, 1H), 5.46 (t, $J$ = 5.30 Hz, 1H), 6.94 (d, $J$ = 2.0 Hz, 1H), 7.04 (dd, $J$ = 2.0, 8.60 Hz, 1H), 7.80 (d, $J$ = 8.60 Hz, 1H); $^{13}C$ NMR ($CDCl_3$ + $CD_3OD$): $\delta$ 54.9, 62.1, 81.1, 105.6, 116.4, 117.8, 126.1, 149.8, 164.5, 170.8; HRMS (ESI) calcd for: $C_{10}H_{10}O_4$ $[M + H]^+$ 195.0657, found 195.0663.

**(*R*)-3-(Hydroxymethyl)-5,6-dimethoxyisobenzofuran-1(3*H*)-one (5o).** Yield: 93%, colorless solid; mp 165–167 °C; 99% ee by chiral HPLC analysis (Chiracel OJ-H, *n*-hexane–iPrOH, 90 : 10, 0.5 mL $min^{-1}$) retention time 23.18 (99.36%) and 27.60 (0.64%); $[\alpha]_{25}^{D}$ −77.89 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 698, 828, 956, 102v7, 1056, 1225, 1266, 1309, 1335, 1474, 1508, 1612, 1752, 2922, 3023, 3358 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): 2.71 (t, $J$ = 6.44 Hz, 1H), 3.81–3.90 (m, 1H), 3.93 (s, 3H), 3.99 (s, 3H), 4.04–4.15 (m, 1H), 5.42–5.47 (m, 1H), 6.93 (s, 1H), 7.25 (s, 1H); $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 56.1, 56.3, 62.4, 81.7, 105.0, 105.8, 117.9, 142.4, 150.4, 154.6, 170.6; HRMS (ESI) calcd for: $C_{11}H_{12}O_5$ $[M + H]^+$ 225.0763, found 225.0772.

**(*R*)-3-(Hydroxymethyl)-6,7-dimethoxyisobenzofuran-1(3*H*)-one (5p).** Yield: 94%, colorless solid; mp 85–88 °C; 99% ee by chiral HPLC analysis (Chiracel OJ-H, *n*-hexane–iPrOH, 90 : 10, 0.5 mL $min^{-1}$) retention time 18.27 (99.36%) and 20.93 (0.64%); $[\alpha]_{25}^{D}$ −78.21 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 698, 798, 956, 1030, 1067, 1220, 1328, 1339, 1458, 1605, 1745, 2976, 3012, 3457 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): 2.24 (brs, 1H), 3.79–3.85 (m, 1H), 3.90 (s, 3H), 3.95 (s, 3H), 4.03–4.09 (m, 1H), 5.35–5.39 (m, 1H), 6.42 (s, 1H), 6.48(s, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 56.6, 62.0, 63.7, 80.7, 116.8, 118.4, 119.4, 139.7, 148.0, 152.5, 168.2; HRMS (ESI) calcd for: $C_{11}H_{12}O_5$ $[M + H]^+$ 225.0718, found 225.0715. HRMS (ESI) calcd for: $C_{11}H_{12}O_5$ $[M + H]^+$ 225.0763, found 225.0772.

**(*R*)-3-(Hydroxymethyl)-5,7-dimethoxyisobenzofuran-1(3*H*)-one (5q).** Yield: 94%, colorless solid; mp 152–153 °C; 99% ee by chiral HPLC analysis (Chiracel OJ-H, *n*-hexane–iPrOH, 90 : 10, 0.5 mL $min^{-1}$) retention time 18.27 (99.36%) and 20.40 (0.64%); $[\alpha]_{25}^{D}$ −78.11 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 695, 765, 950, 1030, 1058, 1232, 1331, 1365, 1463, 1615, 1751, 2982, 3010, 3443 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): 2.53 (brs, 1H), 3.77–3.88 (m, 1H), 3.91 (s, 3H), 3.99–4.04 (m, 3H), 4.10 (s, 1H), 5.40–5.45 (m, 1H), 7.09 (dd, $J$ = 084, 8.20 Hz, 1H), 7.22 (d, $J$ = 8.20 Hz, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 54.7, 54.9, 62.2, 80.4, 97.6, 98.2, 105.9, 151.7, 158.9, 166.6, 168.9; HRMS (ESI) calcd for: $C_{11}H_{12}O_5$ $[M + H]^+$ 225.0763, found 225.0772.

**(*R*)-3-(Hydroxymethyl)-5,6,7-trimethoxyisobenzofuran-1(3*H*)-one (5r).** Yield: 92%, colorless solid; mp 178–180 °C; $[\alpha]_{25}^{D}$ −78.05 (*c* 1.15, $CHCl_3$); IR ($CHCl_3$): 1014, 1097, 1254, 1345, 1483, 1600, 1754, 2947, 3017, 3444 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): 2.62 (brs, 1H), 3.84–3.90 (m, 4H), 3.96 (s, 3H), 4.03–4.09 (m, 1H), 4.13(s, 3H), 5.35–5.39 (m, 1H), 6.69 (s, 1H); $^{13}C$ NMR ($CDCl_3$ + $CD_3OD$): $\delta$ 56.4, 61.2, 62.1, 63.7, 80.6, 99.9, 110.7, 141.8, 144.8, 152.1, 159.7, 168.3; HRMS (ESI) calcd for: $C_{12}H_{14}O_6$ $[M + H]^+$ 255.0869, found 255.0863.

**(*R*)-1,3-Dihydro-1-(hydroxymethyl)-5-methoxy-3-oxoisobenzofuran-6-yl-4-methylbenzenesulfonate (5s).** Yield: 93%, colorless solid; mp 152–154 °C; $[\alpha]_{25}^{D}$ −77.79 (*c* 1.18, $CHCl_3$); IR ($CHCl_3$): 734, 849, 973, 103, 1053, 1178, 1345, 1372, 1494, 1614, 1755, 2919, 3018, 3437 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): 2.24 (brs, 1H), 2.48 (s, 3H), 3.80 (s, 3H), 3.92 (dd, $J$ = 4.60, 12.36 Hz, 1H), 4.03 (dd, $J$ = 4.73, 12.36 Hz, 1H), 5.44 (t, $J$ = 4.60 Hz, 1H), 6.97 (s, 1H), 7.35 (d, $J$ = 8.28 Hz, 2H), 7.48 (s, 1H), 7.78 (d, $J$ = 8.28 Hz, 2H); $^{13}C$ NMR ($CDCl_3$ + $CD_3OD$): $\delta$ 20.1, 55.1, 61.5, 81.0, 105.4, 117.4, 119.3, 127.7, 128.8, 131.9, 138.9, 145.2, 147.8, 156.6, 169.5; HRMS (ESI) calcd for: $C_{17}H_{16}O_7S$ $[M + H]^+$ 365.0695, found 365.0693.

**(*R*)-5-(Benzyloxy)-3-(hydroxymethyl)-6-methoxyisobenzofuran-1(3*H*)-one (5t).** Yield: 94%, colorless solid; mp 126–128 °C; $[\alpha]_{25}^{D}$ −78.22 (*c* 1.10, $CHCl_3$); IR ($CHCl_3$): 689, 825, 975, 1025, 1076, 1223, 1268, 1312, 1334, 1494, 1528, 1621, 1752, 2924, 3032, 3385 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): 2.31 (brs, 1H), 3.75–3.85 (m, 1H), 3.92 (s, 3H), 3.98–4.06 (m, 1H), 5.22 (s, 2H), 5.36–5.41 (m, 1H), 6.92 (s, 1H), 7.28 (s, 1H), 7.32–7.45 (m, 5H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 56.2, 64.1, 71.1, 81.0, 105.4, 106.6, 118.7, 127.3, 128.4, 128.8, 135.6, 140.9, 151.3, 154.0, 170.5; HRMS (ESI) calcd for: $C_{17}H_{16}O_5$ $[M + H]^+$ 301.1076, found 301.1072.

**(*R*)-5-Fluoro-3-(hydroxymethyl)isobenzofuran-1(3*H*)-one (5u).** Yield: 94%, gum; $[\alpha]_{25}^{D}$ −77.21 (*c* 1.21, $CHCl_3$); IR ($CHCl_3$): 689, 825, 975, 1025, 1076, 1223, 1268, 1312, 1334, 1494, 1528, 1621, 1752, 2924, 3032, 3385 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): 2.87 (brs, 1H), 3.93 (dd, $J$ = 4.04, 12.59 Hz, 1H), 4.11

(dd, $J$ = 4.04, 12.59 Hz, 1H), 5.51–5.53 (t, $J$ = 4.04 Hz, 1H), 7.21–7.27 (m, 2H), 7.88–7.91 (m, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 63.5, 80.9, 109.7 (d, $J$ = 24.64 Hz), 117.7 (d, $J$ = 24.64 Hz), 122.6, 128.2 (d, $J$ = 9.48 Hz), 149.7 (d, $J$ = 9.48 Hz), 167.3 (d, $J$ = 398.54 Hz), 167.9; HRMS (ESI) calcd for: $C_9H_7FO_3$ $[M + H]^+$ 183.0457, found 183.0463.

**(*R*)-3-(Hydroxymethyl)-5,6-dioxomethylisobenzofuran-1(3*H*)-one (5v).** Yield: 93%, colorless solid; mp 144–145 °C; $[\alpha]_{25}^{D}$ −78.11 ($c$ 1.20, $CHCl_3$); IR ($CHCl_3$): 698, 852, 957, 1024, 1067, 1232, 1286, 1319, 1343, 1484, 1582, 1612, 1766, 2942, 3054, 3389 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): 2.40 (brs, 1H), 3.84 (dd, $J$ = 4.05, 12.47 Hz, 1H), 4.06 (dd, $J$ = 4.05, 12.47 Hz, 1H), 5.41 (m, 1H), 6.13 (d, $J$ = 2.33 Hz, 2H), 6.87 (s, 1H), 7.20 (s, 1H); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 62.1, 81.3, 102.8, 103.3, 119.8, 144.5, 149.1, 153.3, 169.6; HRMS (ESI) calcd for: $C_{10}H_8O_5$ $[M + H]^+$ 209.0450, found 209.0454.

**(*R*)-3-((*R*)-1-Hydroxybutyl)isobenzofuran-1(3*H*)-one (5w).** Yield: 93%; colorless solid; mp 103–109 °C; $[\alpha]_{25}^{D}$ −76.89 ($c$ 1.0, $CHCl_3$); IR ($CHCl_3$): 694, 728, 1080, 1212, 1287, 1467, 1618, 1752, 2873, 2959, 3433 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.93 (t, $J$ = 6.86 Hz, 3H), 1.44–1.72 (m, 4H), 1.97 (brs, 1H), 3.99 (brs, 1H), 5.40 (d, $J$ = 3.68 Hz, 1H), 7.51–7.57 (m, 2H), 7.65–7.73 (m, 1H), 7.87–7.92 (m, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 13.9, 18.8, 34.9, 71.9, 83.3, 122.5, 125.7, 126.6, 129.3, 134.0, 147.3, 170.5; Analysis: $C_{12}H_{14}O_3$ requires C 69.88, H 6.84 found C 69.82, H 6.81.

**(*R*)-3-((*R*)-1-Hydroxy-2-tertiarybutyldimethylsilylethyl)-5,6-dimethoxyisobenzofuran-1(3*H*)-one (5x).** Yield: 94%, colorless solid; mp 166–168 °C; $[\alpha]_{25}^{D}$ −79.24 ($c$ 1.10, $CHCl_3$); IR ($CHCl_3$): 775, 837, 1060, 1137, 1471, 1503, 1740, 2855, 2926, 3406 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): 0.08 (d, $J$ = 5.45 Hz, 6H), 0.90 (s, 9H), 2.30 (d, $J$ = 5.50 Hz, 1H), 3.62–3.82 (m, 2H), 3.94 (s, 3H), 3.98 (s, 3H), 4.05–4.12 (m, 1H), 5.51 (d, $J$ = 3.49 Hz, 1H), 6.98 (s, 1H), 7.28 (s, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ −5.0, −4.5, 17.9, 25.6, 56.2, 63.2, 73.3, 80.2, 104.2, 106.0, 118.9, 141.6, 150.6, 154.6, 170.6; Analysis: $C_{18}H_{28}O_6Si$ requires C 58.67, H 7.66 found C 58.65, H 7.68%.

**(*R*)-3-((*R*)-Hydroxy(phenyl)methyl)-5,6-dimethoxyisobenzofuran-1(3*H*)-one (5y).** Yield: 94%, colorless solid; mp 113–115 °C; $[\alpha]_{25}^{D}$ −79.23 ($c$ 1.15, $CHCl_3$); IR ($CHCl_3$): 756, 857, 974, 1026, 1064, 1158, 1216, 1334, 1604, 1743, 2858, 2928, 3430 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): 3.05 (brs, 1H), 3.64 (s, 3H), 3.90 (s, 3H), 4.69 (d, $J$ = 7.44 Hz, 1H), 5.47 (d, $J$ = 7.44 Hz, 1H), 5.85 (s, 1H), 7.20 (s, 1H), 7.34–7.41 (m, 5H); $^{13}$C NMR ($CDCl_3$ + $CD_3OD$): $\delta$ 54.7, 74.4, 83.0, 104.3, 117.4, 126.7, 127.4, 138.2, 140.6, 149.8, 153.6, 170.7; Analysis: $C_{17}H_{16}O_5$ requires C 67.99, H 5.37 found C 67.92, H 5.41%.

**(*R*)-3-((*R*)-1-Hydroxyheptyl)-5,6,7-trimethoxyisobenzofuran-1(3*H*)-one (5z).** Yield: 92%, colorless solid; mp 113–115 °C; $[\alpha]_{25}^{D}$ −78.36 ($c$ 1.08, $CHCl_3$); IR ($CHCl_3$): 796, 1089, 1130, 1254, 1326, 1465, 1543, 1749, 2898, 2974, 3988 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): 0.87–0.93 (m, 3H), 1.26–1.37 (m, 8H), 1.64–1.78 (m, 3H), 3.87 (s, 3H), 3.94–3.96 (m, 4H), 4.13 (s, 3H), 5.23 (d, $J$ = 3.09 Hz, 1H), 6.68 (s, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 14.1, 22.5, 25.7, 29.2, 31.7, 32.9, 56.4, 61.3, 62.2, 72.1, 81.7, 99.9, 111.2, 141.8, 145.3, 152.3, 159.6, 168.1; Analysis: $C_{18}H_{26}O_6$ requires C 63.89, H 7.74 found C 63.81, H 7.68%.

**(*S*)-3-((*S*)-Hydroxy(phenyl)methyl)-5,7-dimethoxyisobenzofuran-1-(3*H*)-one (13a).** Yield: 93%; colorless solid; mp 170–172 °C; $[\alpha]_{25}^{D}$ + 78.02 ($c$ 1.20, $CHCl_3$), 99% ee (Mosher's ester analysis); IR ($CHCl_3$): 695, 759, 953, 1045, 1073, 1205, 1331, 1463, 1625, 1754, 2981, 3014, 3440 cm$^{-1}$; $^1$H NMR (500 MHz, MeOH-$d_4$): $\delta$ 3.69 (s, 3H), 3.85 (s, 3H), 4.81 (d, $J$ = 6.41 Hz, 1H), 5.48 (d, $J$ = 6.41 Hz, 1H), 5.87 (d, $J$ = 1.9 Hz, 1H), 6.39 (d, $J$ = 1.9 Hz, 1H), 7.29–7.32 (m, 5H); $^{13}$C NMR ($CDCl_3$ + $CD_3OD$): $\delta$ 56.3, 76.0, 84.1, 100.0, 100.2, 107.8, 128.3, 128.9, 129.2, 139.5, 152.3, 160.2, 167.4, 170.2; HRMS (ESI) calcd for: $C_{17}H_{16}O_5$ $[M + H]^+$ 301.1076, found 301.1081.

**(*R*)-3-((*R*)-Hydroxy(phenyl)methyl)-5,7-dimethoxyisobenzofuran-1-(3*H*)-one (13b).** Yield: 93%; colorless solid; mp 170–172 °C; $[\alpha]_{25}^{D}$ −77.56 ($c$ 1.15, $CHCl_3$), 99% ee (Mosher's ester analysis); IR ($CHCl_3$): 698, 759, 947, 1041, 1077, 1204, 1336, 1461, 1625, 1754, 2981, 3018, 3444 cm$^{-1}$ cm$^{-1}$; $^1$H NMR (500 MHz, MeOH-$d_4$): $\delta$ 3.61 (s, 3H), 3.84 (s, 3H), 4.77 (d, $J$ = 6.41 Hz, 1H), 5.45 (d, $J$ = 6.41 Hz, 1H), 5.78(d, $J$ = 1.7 Hz, 1H), 6.35 (d, $J$ = 1.7 Hz, 1H), 7.29–7.32 (m, 5H); $^{13}$C NMR ($CDCl_3$ + $CD_3OD$): $\delta$ 56.1, 76.0, 83.9, 99.9, 102.9, 107.6, 128.2, 128.8, 129.0, 139.2, 152.0, 159.9, 167.1, 169.8; HRMS (ESI) calcd for: $C_{17}H_{16}O_5$ $[M + H]^+$ 301.1076, found 301.1081.

**(*S*)-3-((*S*)-1-Hydroxyethyl)-5,7-dimethoxyisobenzofuran-1(3*H*)-one (15).** Yield: 93%; colorless solid; mp 139–140 °C; $[\alpha]_{25}^{D}$ + 76.89 ($c$ 1.10, $CHCl_3$); IR ($CHCl_3$): 692, 771, 954, 1036, 1063, 1237, 1329, 1361, 1454, 1611, 1725, 2986, 3008, 3447 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 1.33 (d, $J$ = 6.4 Hz, 3H), 2.0 (brs, 1H), 3.88 (s, 3H), 3.94 (s, 3H), 4.09–4.15 (m, 1H), 5.17(d, $J$ = 3.99 Hz, 1H), 6.42 (d, $J$ = 1.8 Hz, 1H), 6.52 (d, $J$ = 1.8 Hz, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 18.7, 55.9, 68.6, 82.6, 98.3, 99.1, 107.5, 151.9, 159.7, 166.7, 168.0; HRMS (ESI) calcd for: $C_{12}H_{14}O_5$ $[M + H]^+$ 239.0919, found 239.0923.

**(+) Matteucen C (2a).** Yield: 68%; colorless powder; $[\alpha]_{25}^{D}$ + 54.18 ($c$ 1.0, MeOH); IR ($CHCl_3$): 691, 710, 1169, 1615, 1684, 1725, 3364 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 4.94 (t, $J$ = 4.8 Hz, 1H), 5.44 (d, $J$ = 4.0 Hz, 1H), 5.72 (d, $J$ = 4.8 Hz, 1H), 6.23 (d, $J$ = 1.8 Hz, 1H), 6.25 (d, $J$ = 1.8 Hz, 1H), 7.24–7.36 (m, 5H), 10.29 (s, 1H), 10.31 (s, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 72.6, 81.7, 101.1, 102.3, 104.2, 126.9, 127.2, 127.6, 140.7, 151.5, 157.6, 163.9, 167.7; HRMS (ESI) calcd for: $C_{15}H_{12}O_5$ $[M + H]^+$ 273.0763, found 273.0766.

**(−) Matteucen C (2b).** Yield: 68%; colorless powder; $[\alpha]_{25}^{D}$ −54.16 ($c$ 1.0, MeOH); IR ($CHCl_3$): 691, 710, 1169, 1615, 1684, 1725, 3364 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 4.94 (t, $J$ = 4.8 Hz, 1H), 5.44 (d, $J$ = 4.0 Hz, 1H), 5.73 (d, $J$ = 4.8 Hz, 1H), 6.23 (d, $J$ = 1.8 Hz, 1H), 6.25 (d, $J$ = 1.8 Hz, 1H), 7.27–7.36 (m, 5H), 10.30 (s, 1H), 10.33 (s, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 72.6, 81.7, 101.1, 102.3, 104.2, 126.9, 127.3, 127.6, 140.7, 151.5, 157.6, 163.9, 167.7; HRMS (ESI) calcd for: $C_{15}H_{12}O_5$ $[M + H]^+$ 273.0763, found 273.0766.

**3-Butylphthalide (3).** Yield: 86%; Colourless oil; $[\alpha]_{25}^{D}$ −62.1 ($c$ 1.15, $CHCl_3$, ee = 99%); lit.,[2i] $[\alpha]_{22}^{D}$ −62 ($c$ 4.2, $CHCl_3$, ee = 99%); IR ($CHCl_3$): 780, 1346, 1465, 1526, 1716, 2932 cm$^{-1}$; $^1$H

NMR (200 MHz, $CDCl_3$): $\delta$ 0.88–0.95 (m, 3H), 1.32–1.53 (m, 4H), 1.68–1.86 (m, 1H), 1.97–2.07 (m, 1H), 5.46 (q, $J$ = 7.6 Hz, 1H), 7.42 (dd, $J$ = 1.13, 7.6 Hz, 1H), 7.52 (t, $J$ = 7.4 Hz, 1H), 7.66 (td, $J$ = 1.13, 7.4 Hz, 1H), 7.90 (d, $J$ = 7.6 Hz, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 13.9, 22.4, 26.9, 34.4, 81.3, 121.9, 125.5, 129.0, 133.9, 150.1, 170.3; HRMS (ESI) calcd for: $C_{12}H_{14}O_2$ $[M + H]^+$ 191.1072, found 191.1069.

### Demethyl pestaphthalide (16)

Yield: 78%; colorless solid; mp 102–104 °C; $[\alpha]_{25}^{D}$ + 61.4 (*c* 0.50, MeOH, ee = 99%); lit.,[7b] $[\alpha]_{19}^{D}$ + 60.7 (*c* 0.29, MeOH); IR ($CHCl_3$): 1060, 1164, 1220, 1280, 1330, 1360, 1480, 1620, 1710, 1730 $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.03 (d, $J$ = 6.4 Hz, 3H), 4.0 (m, 1H), 4.91 (brs, 1H), 5.13(d, $J$ = 3.0 Hz, 1H), 6.27 (brs, 1H), 6.36 (brs,1H), 10.28 (br, 2H); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 18.4, 66.3, 81.8, 100.9, 102.4, 104.2, 152.1, 157.8, 164.2, 168.0; HRMS (ESI) calcd for: $C_{10}H_{10}O_5$ $[M + H]^+$ 211.0606, found 211.0612.



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