Synthesis of (*S*)-3-Heteroaryl-2-hydroxy-1-propyl Benzoates by 'Ring Switching' Methodology

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Dedicated to Professor Jerald S. Bradshaw, Brigham Young University, Provo, Utah, on the Occasion of his 70th Birthday

(*S*)-5-Benzoyloxymethyl-3-[(*E*)-(dimethylamino)methylidene]tetrahydrofuran-2-one (**6**), prepared in 5 steps from L-glutamic acid (**1**), was used as precursor in a one step 'ring switching' synthesis of (*S*)-2-hydroxy-3-heteroaryl-1-propyl benzoates **13**–**18**, **23**, **24**. In the reaction of **6** with 2-aminopyridine (**21**) and 2-amino-4,6-dimethylpyrimidine (**22**) the corresponding dimethylamine substitution products (**25**, **26**) were obtained.

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Chiral hydroxy compounds, such as alcohols, diols, polyols, and hydroxy acids, have found a wide aplicability in organic synthesis, especially as chiral building blocks, chiral auxilliaries, and resolving agents. Many examples of synthetically important carbo- and heterocyclic hydroxy compounds are found among carbohydrates, amino- and hydroxy acids, terpenes and terpenoids, and alkaloids [1].

5-Substituted (*S*)-3-[(*E*)-(dimethylamino)methylidene]-pyrrolidin-2-ones and (*S*)-3-[(*E*)-(dimethylamino)-methylidene]tetrahydrofuran-2-ones, chiral cyclic analogs of alkyl 2-substituted 3-(dimethylamino)propenoates [2], have been successfully employed as precursors for the preparation of 3-heteroarylalanine- [3,4], 3-heteroaryl-lalaninol- [5], 3-heteroaryllactic acid derivatives [6], and their analogs [7,8]. In this connection, Young and coworkers have been the first demonstrating that 3-heteroarylalanine derivatives can be prepared from (*S*)-1-acyl-5-(alkoxycarbonyl)-3-[(dimethylamino)methylidene]pyrrolidin-2-ones *via* hydrolysis to the corresponding 3-formyl derivatives followed by 'ring switching' transformation with various ambident nucleophiles [3]. On the other hand, we have shown that a 'ring switching' formation of 3-heteroarylalanine derivatives can also be achieved directly from (*S*)-1-benzoyl-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one by treatment with ambident nucleophiles in acetic acid at elevated temperature [4]. The same synthetic methodology has been applied to the preparation of heteroarylalaninol- and heteroaryllactic acid derivatives [5,6] (Figure 1).

In continuation of our work in this field, we report a modified preparation of (*S*)-5-benzoyloxymethyl-3-[(*E*)-(dimethylamino)methylidene]tetrahydrofuran-2-one (**6**) and its 'ring switching' transformations into various (*S*)-3-heteroaryl-2-hydroxy-1-propyl benzoates **13**–**18**, **23**, **24** as

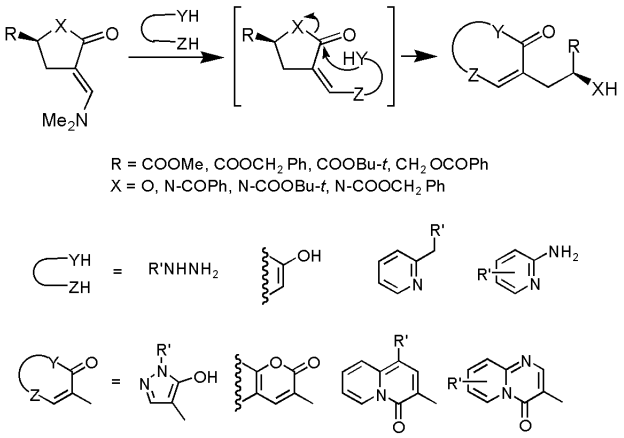
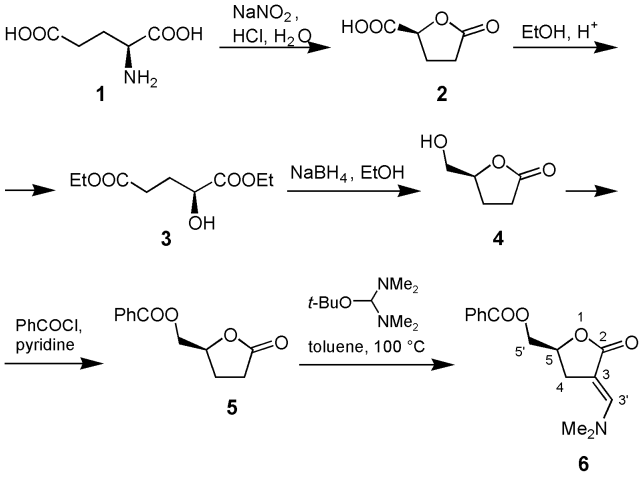


Figure 1. 'Ring Switching' transformations of γ-substituted (*S*)-α-[(*E*)-(dimethylamino)methylidene]- γ-lactams and γ-lactones.

3-heteroarylpropane-1,2-diol derivatives. Starting compound, (*S*)-5-benzoyloxymethyl-3-[(*E*)-(dimethylamino)-methylidene]tetrahydrofuran-2-one (**6**), was prepared from (*S*)-5-(benzoyloxymethyl)tetrahydrofuran-2-one (**5**) according to a slightly modified procedure described previously [7]. Compound **5** has been prepared by benzoylation of commercially available, but rather expensive (*S*)-5-(hydroxymethyl)tetrahydrofuran-2-one (**4**) [9a], which, on the other hand, is also available in three steps from L-glutamic acid (**1**) [9,10]. For our purpose, a slightly modified procedure was employed for the preparation of (*S*)-5-(benzoyloxymethyl)tetrahydrofuran-2-one (**5**), which was then treated with bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent) to afford (*S*)-5-benzoyloxymethyl-3-[(*E*)-(dimethylamino)methylidene]tetrahydrofuran-2-one (**6**) in 36% overall yield from **1** (Scheme 1).

Scheme 1



(*S*)-5-Benzoyloxymethyl-3-[(*E*)-(dimethylamino)-methylidene]tetrahydrofuran-2-one (**6**) was treated with the following *C*,*N*- and *C*,*O*-ambident nucleophiles: ethyl 2-pyridinylacetate (**7**), 2-pyridinylacetonitrile (**8**), 5,5-dimethylcyclohexane-1,3-dione (**9**), 2,3-dihydroxynahpthalene (**10**), 4-hydroxy-6-methyl-2*H*-pyran-2-one (**11**), and 4-hydroxy-2*H*-benzo[*b*]pyran-2-one (**12**). Reactions were carried out in acetic acid at 110 °C to give 'ring switched' chiral propane-1,2-diols **13**–**18** with a quinolizine- or a fused 2*H*-pyran-2-one system attached at the 3–position. Thus, treatment of **6** with ethyl 2-pyridinylacetate (**7**) and 2-pyridinylacetonitrile (**8**) as *C*,*N*-ambident nucleophiles gave (*S*)-3-(1-substituted 4-oxo-4*H*-quinolizin-3-yl)-2-hydroxy-1f-propyl benzoates (**13**, **14**), while with *C*,*O*-ambident nucleophiles

Scheme 2

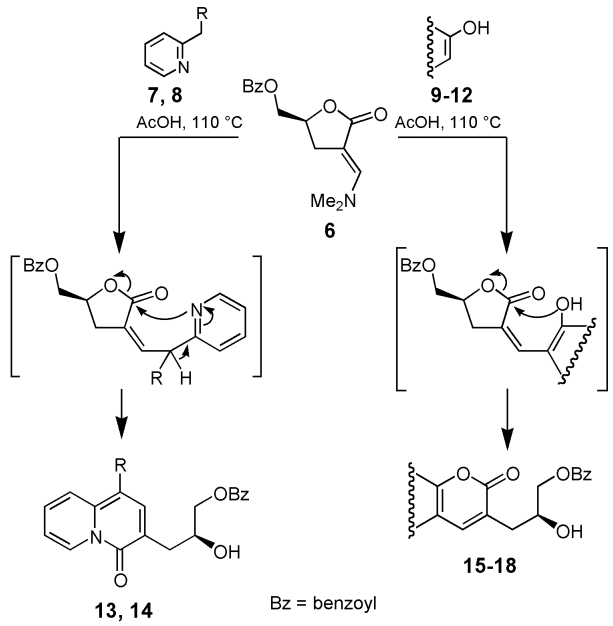
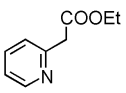
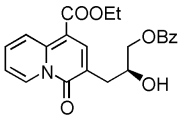
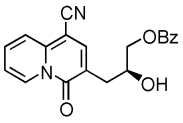
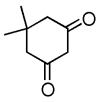
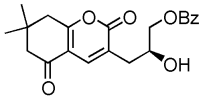
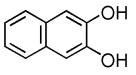
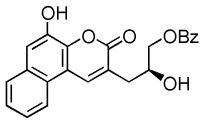
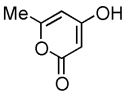
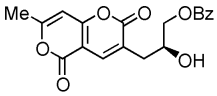
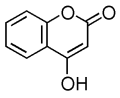
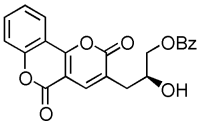


Table 1

Reactions of **6** with *C*,*N*- and *C*,*O*-Ambident Nucleophiles (**7**–**12**)

Nucleophile	→	Product	Yield (%)
 **7**		 **13**	18
 **8**		 **14**	46
 **9**		 **15**	81
 **10**		 **16**	14
 **11**		 **17**	33
 **12**		 **18**	37

9–**12** the corresponding (*S*)-2-hydroxy-3-(fused 2-oxo-2*H*-pyran-3-yl)-1-propyl benzoates (**15**–**18**) were obtained in 14–81% yields (Scheme 2, Table 1).

Similarly, treatment of **6** with 2-hydrazinopyridine (**19**) and 3-hydrazino-6-phenylpyridazine (**20**) as *N*,*N'*-ambident nucleophiles in acetic acid at 110 °C resulted in the formation of the pyrazole ring to give (*S*)-2-hydroxy-3-[5-hydroxy-1-(pyridin-2-yl)-1*H*-pyrazol-4-yl]-1-propyl benzoate (**23**) and (*S*)-2-hydroxy-3-[5-hydroxy-1-(6-phenylpyridazin-3-yl)-1*H*-pyrazol-4-yl]-1-propyl benzoate (**24**) in 19% and 32% yield, respectively. Under the same conditions, only the substitution of the dimethylamino group took place upon reaction of the furanone **6** with 2-aminopyridine (**21**) and 2-amino-4,6-dimethylpyrimidine (**22**) to afford the corresponding (*S*)-5-benzoyloxymethyl-3-(heteroarylaminomethylidene)tetrahydrofuran-2-ones **25** and **26** in 44 and 45% yield, respectively (Scheme 3, Table 2).

Scheme 3

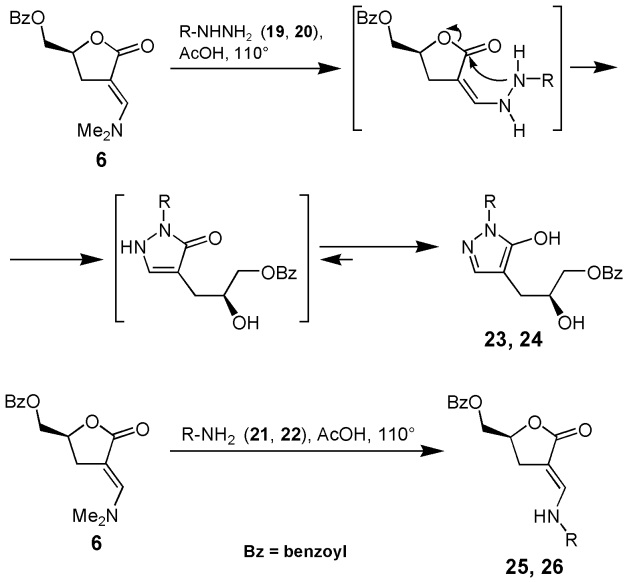
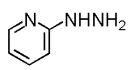
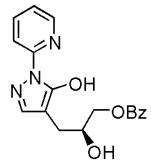
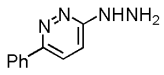
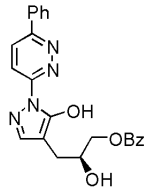
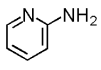
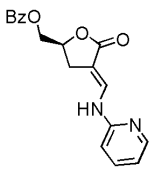
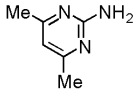
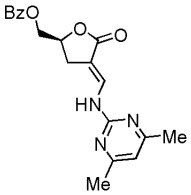


Table 2

Reactions of **6** with *N,N'*-Ambident Nucleophiles (**19**–**22**)

Nucleophile	→	Product	Yield (%)
 **19**		 **23**	19
 **20**		 **24**	32
 **21**		 **25**	44
 **22**		 **26**	45

Structures of products **13**–**18**, **23**–**26** were determined by spectroscopic methods (NMR, IR, MS) and elemental analyses for C, H, and N. Spectral data for compounds **13**–**18**, **23**–**26** are in agreement with the data of closely related 3-(heteroaryl)alanine-, 3-(heteroaryl)alaninol-, and 3-(heteroaryl)lactic acid derivatives [2–8]. The (*E*)-configuration around the exocyclic C=C double in compound **6**, determined by nmr (ROESY technique), is in accordance with the general orientation in 3-(dimethylamino)propenoate series, where the dimethylamino group is *trans*-oriented with respect to the ester group [2] (Figure 2).

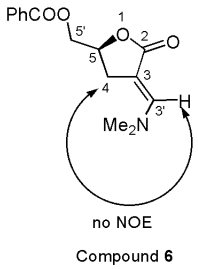


Figure 2. Nmr (ROESY) determination of configuration around the C=C double bond in compound **6** (deuteriochloroform, 25 °C).

EXPERIMENTAL

All starting materials were commercially available (in most cases from Fluka AG) and purified following standard techniques. Column chromatography: silica gel, silica gel 60, 0.04–0.06 mm (Fluka). Tlc: alu foils coated with silica gel 60 F 254, 0.2 mm (Merck). Mp: Kofler micro hot stage. Optical rotations: Perkin-Elmer 241 MC polarimeter. ^{1}H nmr (300 MHz) and ^{13}C nmr (75.5 MHz): Bruker Avance DPX 300 spectrometer with deuteriochloroform and dimethyl sulfoxide–d_6 as solvents and tetramethylsilane as internal standard. Ir: Perkin-Elmer Spectrum BX FTIR spectrometer (KBr). Ms: Autospeck Q (VG-Analytical) spectrometer. Elemental analyses for C, H, and N: Perkin-Elmer CHN Analyser 2400.

Preparation of (*S*)-5-(Benzoyloxymethyl-3-[(*E*)-(dimethylamino)methylidene]tetrahydrofuran-2-one (**6**).

This compound was prepared in 4 steps from L-glutamic acid (**1**) by modified procedures described in the literature [7,9,10].

Diethyl (*S*)-2-Hydroxypentane-1,5-dioate (**3**).

A solution of $NaNO_2$ (8.28 g, 0.12 mole) in water (22 mL) was added dropwise at 0–5 °C to a stirred mixture of L-glutamic acid (**1**) (14.7 g, 0.1 mole), water (40 ml), and hydrochloric acid (37%, 21 ml). After the addition was complete, the reaction mixture was stirred at room temperature for 12 hours. Volatile components were evaporated *in vacuo* at 40–50 °C and the residue was triturated with hot ethyl acetate (3 x 100 ml). Each time, the hot ethyl acetate solution was decanted from the undissolved solid. Ethyl acetate solutions were combined, cooled to room temperature, dried over anhydrous sodium sulfate, filtered, and the filtrate evaporated *in vacuo* to

give crude (*S*)-tetrahydrofuran-2-one-5-carboxylic acid (**2**). The crude compound **2** (11.37 g, 0.087 mole) was dissolved in anhydrous ethanol (100 ml), sulfuric acid (97%, 5 ml) was added, and the solution was left at room temperature for 48 hours. The reaction mixture was then poured carefully into saturated aqueous sodium bicarbonate (200 ml) and the product was extracted with dichloromethane (first 200 ml, then 2 x 100 ml). Organic phases were combined, dried over anhydrous sodium sulfate, filtered , and the filtrate evaporated *in vacuo*. The residue was distilled (Kugelrohr) at 180 °C/12 mm to give the crude compound **3** [11]. Yield: 10.203 g (50%). $[\alpha]_D^{22}$ –3.3° (*c* = 1.07, ethanol); lit [9b] $[\alpha]_D^{20}$ –3.9° (*c* = 0.3, ethanol). ^{1}H nmr (deuteriochloroform): δ 1.21–1.36 (6H, *m*, 2 Me); 1.87–1.99 (1H, *m*, H–C(3)); 2.11–2.24 (1H, *m*, H–C(3)); 2.25–2.68 (2H, *m*, 2 H–C(4)); 2.97 (1H, *br s*, OH); 4.08–4.33 (5H, *m*, 2 OCH_2 and H–C(2)).

(*S*)-5-(Hydroxymethyl)tetrahydrofuran-2-one (**4**).

The crude compound **3** from previous experiment (10.203 g, 50 mmol) was dissolved in anhydrous ethanol (50 ml) and this solution was added dropwise to a stirred suspension of sodium borohydride (2.204 g, 58 mmol) in anhydrous ethanol (50 ml) at 20–25 °C. The reaction mixture was stirred at room temperature for 2 hours, cooled to 0–5 °C, acidified with hydrochloric acid (10%) to pH 3, filtered, and the filtrate evaporated *in vacuo*. Methanol (30 ml) was added to the residue and the mixture was evaporated *in vacuo* (4 times). The residue was purified by flash column chromatograpy (chloroform/ethanol, 93:7, ~400 ml, column dimensions: 3 x 15 cm). The eluate was evaporated *in vacuo* and the residue was distilled (Kugelrohr) at 160 °C/1 mm to give (*S*)-5-(hydroxymethyl)tetrahydrofuran-2-one (**4**). Yield: 5.028 g (86%), lit [9b] yield: 70%. $[\alpha]_D^{22}$ +27.7° (*c* = 1.03, ethanol); lit [9a] $[\alpha]_D^{26}$ +31.3° (*c* = 2.92, ethanol); lit [9b] $[\alpha]_D^{20}$ +29.6° (*c* = 0.4, ethanol). ^{1}H nmr (deuteriochloroform): δ 2.08–2.34 (2H, *m*, H–C(4)); 2.47–2.70 (2H, *m*, H–C(3)); 3.65 (1H, *dd*, *J* = 4.5, 12.4 Hz, H–C(5')); 3.90 (1H, *dd*, *J* = 3.0, 12.4 Hz, H–C(5')); 4.60–4.68 (1H, *m*, H–C(5)).

(*S*)-5-(Benzoyloxymethyl)tetrahydrofuran-2-one (**5**).

Compound **4** from previous experiment (5.028 g, 43.30 mmol) was dissolved in anhydrous pyridine (43 ml), benzoyl chloride (5.0 ml, ~90 mmol) was added, and the mixture was stirred at room temperature for 12 hours. Volatile components were evaporated *in vacuo*, toluene (50 ml) was added and the mixture was evaporated *in vacuo*. The residue was dissolved in ether (300 ml) and the solution was washed with water (100 ml), aqueous sodium bicarbonate (5%, 150 ml), water (100 ml), hydrochloric acid (10%, 150 ml), and water (100 ml). Organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography (column dimensions: 3 x 15 cm). First, the non-polar impurities were eluted with ethyl acetate/petroleum ether (1:4) followed by elution of the product with ethyl acetate/petroleum ether (1:1). Fractions containing the product were combined and evaporated *in vacuo* to give analytically pure compound **5**. Yield: 9.41 g (99%), lit [9a] yield: 97%, m.p. 58–59 °C; lit [9a] m.p. 59–60.5 °C. $[\alpha]_D^{22}$ +43.8° (*c* = 0.65, ethanol); lit [9a] $[\alpha]_D^{26}$ +48.2° (*c* = 1.03, ethanol). ^{1}H nmr (deuteriochloroform): δ 2.06–2.21 (1H, *m*, H–C(4)); 2.36–2.50 (1H, *m*, H–C(4)); 2.51–2.72 (2H, *m*, 2 H–C(3)); 4.45 (1H, *dd*, *J* = 5.3, 12.1 Hz, H–C(5')); 4.55 (1H, *dd*, *J* = 3.2, 12.2 Hz, H–C(5')); 4.83–4.92 (1H, *m*, H–C(5)); 7.41–7.50 (2H, *m*, 2H of Ph); 7.54–7.63 (1H, *m*, 1H of Ph); 7.99–8.07 (2H, *m*, 2H of Ph).

Anal. Calcd. for $C_{12}H_{12}O_4$ (220.22): C, 65.45; H, 5.49. Found: C, 65.18; H, 5.74.

(*S*)-5-(Benzoyloxymethyl-3-[(*E*)-(dimethylamino)methylidene])tetrahydrofuran-2-one (**6**).

This compound was prepared by a modified procedure described in the literature [7].

A mixture of **5** (2.20 g, 10 mmol), anhydrous toluene (20 ml), and bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent) (2.610 g, 15 mmol) was stirred under argon at 100–110 °C for 2 hours. Volatile components were evaporated *in vacuo*, the solid residue was purified by column chromatography (column dimensions: 3 x 10 cm). First, the non-polar impurities were eluted with ethyl acetate/petroleum ether (1:1) followed by elution of the product with with ethyl acetate. Fractions containing the product were combined and evaporated *in vacuo* to give **6**. Yield: 2.274 g (83%), lit [7] yield: 43%, m.p. 113–115 °C (from toluene), lit [7] m.p. 109–111 °C (from ethyl acetate/cyclohexane). $[\alpha]_D^{20}$ +121° (*c* = 1.02, dichloromethane), $[\alpha]_D^{22}$ +169° (*c* = 0.73, ethanol); lit [7] $[\alpha]_D^{21}$ +252° (*c* = 1.00, ethanol).

General Procedure for the Preparation of (*S*)-3-Heteroaryl-2-hydroxy-1-pyropyl Benzoates **13–18**, **23**, **24** and (*S*)-5-(Benzoyloxymethyl)-3-(heteroarylaminomethylidene)tetrahydrofuranones **25**, **26**.

A mixture of (*S*)-5-(benzoyloxymethyl-3-[(*E*)-(dimethylamino)-methylidene])tetrahydrofuran-2-one (**6**) (0.275 g, 1 mmol), ambident nucleophile (**7–12**, **19–22**) (1 mmol) and acetic acid (100%, 4 ml) was stirred at 110 °C for 2–7 hours. Volatile components were evaporated *in vacuo*, the residue was triturated with an appropriate solvent, and the precipitate was collected by filtration to give compounds **14**, **16**, **23–26**. In some cases, the residue was purified by column chromatography, fractions containing the product were combined, evaporated *in vacuo*, and the residue was crystallized from an appropriate solvent to give compounds **13**, **15**, **17**, **18**. The following compounds were prepared in this manner:

(*S*)-3-(1-Ethoxycarbonyl-4-oxo-4*H*-quinolizin-3-yl)-2-hydroxy-1-pyropyl Benzoate (**13**).

This compound was prepared from ethyl 2-pyridinylacetate (**7**), heating for 5 hours, column chromatography (ethyl acetate/petroleum ether, 1:1). Yield: 0.072 g (18%), m.p. 98–99 °C (from diethyl ether). $[\alpha]_D^{21}$ +7.5° (*c* = 0.10, CH_2Cl_2). IR(cm^{-1}): 1727, 1619 (C=O). ^{1}H nmr (deuteriochloroform): δ 1.37 (3H, *t*, *J* = 7.2 Hz, CH_3); 3.03–3.19 (2H, *m*, 2 H–C(3)); 4.29–4.45 (5H, *m*, OCH_2, 2 H–C(1), and H–C(2)); 7.21 (1H, *deg dt*, *J* = 1.5, 6.4 Hz, H–C(7')); 7.39–7.47 (2H, *m*, 2H of Ph); 7.51–7.59 (1H, *m*, 1H of Ph); 7.63 (1H, *ddd*, *J* = 1.5, 6.8, 9.4 Hz, H–C(8')); 8.03–8.10 (2H, *m*, 2H of Ph); 8.39 (1H, *s*, H–C(2')); 9.22–9.32 (2H, *m*, H–C(6') and H–C(9')).

Anal. Calcd. for $C_{22}H_{21}NO_6$ (395.41): C, 66.83; H, 5.35; N, 3.54. Found: C, 67.14; H, 5.00; N, 3.37.

(*S*)-3-(1-Cyano-4-oxo-4*H*-quinolizin-3-yl)-2-hydroxy-1-pyropyl Benzoate (**14**).

This compound was prepared from 2-pyridinylacetonitrile (**8**), heating for 7 hours, trituration with ethyl acetate. Yield: 0.160 g (46%), m.p. 143–144 °C (from ethyl acetate). $[\alpha]_D^{21}$ +170° (*c* = 0.50, dichloromethane). IR(cm^{-1}): 3384 (OH), 2214 (CN), 1717 (C=O). ^{1}H nmr (dimethyl sulfoxide–d_6): δ 2.78 (1H, *dd*, *J* = 7.0,

13.4 Hz, H–C(3)); 2.92 (1H, *dd*, *J* = 5.3, 13.6 Hz, H–C(3)); 4.18–4.26 (3H, *m*, 2 H–C(1) and H–C(2)); 5.14 (1H, *br d*, *J* = 5.3 Hz, OH); 7.37–51 (3H, *m*, H–C(7') and 2H of Ph); 7.62 (1H, *tt*, *J* = 1.3, 7.5 Hz, 1H of Ph); 7.87–7.94 (4H, *m*, 2H of Ph, H–C(8'), and H–C(9)); 8.06 (1H, *s*, H–C(2')); 9.10 (1H, *d*, *J* = 7.15 Hz, H–C(6')).

Anal. Calcd. for $C_{20}H_{16}N_2O_4$ (348.36): C, 68.96; H, 4.63; N, 8.04. Found: C, 68.69; H, 4.63; N, 7.93.

(*S*)-3-(7,7-Dimethyl-2,5-dioxo-5,6,7,8-tetrahydro-2*H*-benzo[*b*]pyran-3-yl)-2-hydroxy-1-pyropyl Benzoate (**15**).

This compound was prepared from 5,5-dimethylcyclohexane-1,3-dione (**9**), heating for 7 hours, column chromatography (ethyl acetate/petroleum ether, 1:1). Yield: 0.299 g (81%), oil. $[\alpha]_D^{21}$ +25.0° (*c* = 0.10, dichloromethane). MS (EI): *m/z* = 370 (M^+). ^{1}H nmr (dimethyl sulfoxide–d_6): δ 1.14 (6H, *s*, 2 Me–C(7')); 2.40, 2.70 (2 x 2H, 2*s*, 2 H–C(6') and 2 H–C(8')); 2.71 (1H, *dd*, *J* = 7.9, 12.6 Hz, H–C(3)); 2.84 (1H, *dd*, *J* = 2.8, 14.5 Hz, H–C(3)); 4.29–4.47 (3H, *m*, 2 H–C(1) and H–C(2)); 7.42–7.50 (2H, *m*, 2H of Ph); 7.59 (1H, *tt*, *J* = 1.3, 7.5 Hz, 1H of Ph); 7.81 (1H, *s*, H–C(4')); 8.02–8.08 (2H, *m*, 2H of Ph). ^{13}C nmr (deuteriochloroform): δ 28.6, 28.7, 33.0, 41.8, 50.8, 68.5, 68.8, 114.1, 123.6, 128.8, 130.0, 130.1, 133.6, 137.7, 162.7, 167.0, 171.8, 194.6.

Anal. Calcd. for $C_{21}H_{22}O_6$ (370.40) x 1/2H_2O: C, 66.48; H, 6.11. Found: C, 66.14; H, 6.46. HRMS Calcd. for $C_{21}H_{22}O_6$: 370.141639. Found: 370.142850.

(*S*)-2-Hydroxy-3-(10-hydroxy-2-oxo-2*H*-naphtho[2,1–*b*]pyran-3-yl)-1-pyropyl Benzoate (**16**).

This compound was prepared from 2,3-dihydroxynaphthalene (**10**), heating for 5 hours, trituration with dichloromethane. Yield: 0.056 g (14%), m.p. 198–200 °C (from dichloromethane). $[\alpha]_D^{22}$ –10° (*c* = 0.11, ethyl acetate). IR (cm^{-1}): 3347 (OH), 1724, 1699 (C=O). ^{1}H nmr (dimethyl sulfoxide–d_6): δ 2.79 (1H, *dd*, *J* = 7.5, 13.6 Hz, H–C(3)); 2.91 (1H, *dd*, *J* = 4.5, 13.5 Hz, H–C(3)); 4.28–4.32 (3H, *m*, 2 H–C(1) and H–C(2)); 5.25 (1H, *br s*, HO–C(2)); 7.42 (1H, *s*, H–C(9')); 7.46–7.51 (4H, *m*, 2H of Ph, H–C(6'), and H–C(7')); 7.64 (1H, *tt*, *J* = 1.3, 7.5 Hz, 1H of Ph); 7.79–7.83 (1H, *m*, H–C(8')); 7.95–8.00 (2H, *m*, 2H of Ph); 8.34–8.39 (1H, *m*, H–C(5')); 8.75 (1H, *s*, H–C(4')); 10.23 (1H, *br s*, HO–C(10')).

Anal. Calcd. for $C_{23}H_{18}O_6$ (390.39): C, 70.76; H, 4.65. Found: C, 70.42; H, 4.65.

(*S*)-3-(2,5-Dioxo-7-methyl-2*H*,5*H*-pyrano[4,3–*b*]pyran-3-yl)-2-hydroxy-1-pyropyl Benzoate (**17**).

This compound was prepared from 4-hydroxy-6-methyl-2*H*-pyran-2-one (**11**), heating for 5 hours, column chromatography (ethyl acetate/petroleum ether, 2:1). Yield: 0.117 g (33%), m.p. 92–96 °C (from ethyl acetate). $[\alpha]_D^{21}$ –24.0° (*c* = 0.20, dichloromethane). IR(cm^{-1}): 3517, 3463 (OH), 1748, 1729, 1702 (C=O). ^{1}H nmr (deuteriochloroform): δ 2.35 (3H, *s*, Me–C(7')); 2.74 (1H, *dd*, *J* = 7.9, 14.9 Hz, H–C(3)); 2.87 (1H, *dd*, *J* = 2.8, 14.5 Hz, H–C(3)); 4.29–4.49 (3H, *m*, 2 H–C(1) and H–C(2)); 6.17 (1H, *s*, H–C(4')); 7.42–7.49 (2H, *m*, 2H of Ph); 7.59 (1H, *tt*, *J* = 1.3, 7.5 Hz, 1H of Ph); 7.81 (1H, *s*, H–C(8')); 8.03–8.08 (2H, *m*, 2H of Ph).

Anal. Calcd. for $C_{19}H_{16}O_7$ (356.33): C, 64.04; H, 4.53. Found: C, 64.04; H, 4.60.

(*S*)-3-(2,5-Dioxo-2*H*,5*H*-benzo[*b*]pyrano[4,3–*b*]pyran-3-yl)-2-hydroxy-1-pyropyl Benzoate (**18**).

This compound was prepared from 4-hydroxy-2*H*-benzo[*b*]-pyran-2-one (**12**), heating for 3 hours, column chromatography (ethyl acetate/petroleum ether, 2:1). Yield: 0.145 g (37%), m.p. 87–90 °C (from ethyl acetate). $[\alpha]_D^{21}$ –23.7° (*c* = 0.19, dichloromethane). IR(cm^{-1}): 3502 (OH), 1724 (C=O). ^{1}H nmr (deuteriochloroform): δ 2.61 (1H, *br s*, HO–C(2)); 2.81 (1H, *dd*, *J* = 7.5, 14.3 Hz, H–C(3)); 2.94 (1H, *dd*, *J* = 3.0, 14.3 Hz, H–C(3)); 4.37–4.41 (2H, *m*, H–C(1) and H–C(2)); 4.46–4.53 (1H, *m*, H–C(1)); 7.36–7.47 (4H, *m*, 2H of Ph, H–C(7'), and H–C(9')); 7.56 (1H, *tt*, *J* = 1.3, 7.5 Hz, 1H of Ph); 7.63–7.72 (1H, *m*, H–C(8')); 7.96 (1H, *s*, H–C(4')); 8.01–8.07 (2H, *m*, 2H of Ph).

Anal. Calcd. for $C_{22}H_{16}O_7$ (392.37): C, 67.35; H, 4.11. Found: C, 66.98; H, 4.01.

(*S*)-2-Hydroxy-3-[5-hydroxy-1-(pyridin-2-yl)-1*H*-pyrazol-4-yl]-1-pyropyl Benzoate (**23**).

This compound was prepared from 2-hydrazinopyridine (**19**), heating for 2 hours, trituration with ethyl acetate. Yield: 0.064 g (19%), m.p. 149–151 °C (from ethyl acetate). $[\alpha]_D^{22}$ –3.9° (*c* = 0.33, dichloromethane). IR(cm^{-1}): 3287 (OH), 1714 (C=O). ^{1}H nmr (deuteriochloroform): δ 2.64 (1H, *br s*, HO–C(2)); 2.71 (1H, *dd*, *J* = 6.9, 14.7 Hz, H–C(3)); 2.78 (1H, *dd*, *J* = 5.3, 14.7 Hz, H–C(3)); 4.20–4.28 (1H, *m*, H–C(2)); 4.35 (1H, *dd*, *J* = 6.2, 11.5 Hz, H–C(1)); 4.44 (1H, *dd*, *J* = 3.9, 11.3 Hz, H–C(1)); 7.15–7.20 (1H, *m*, H–C(5")); 7.40–7.47 (3H, *m*, 2H of Ph, H–C(3'))); 7.56 (1H, *tt*, *J* = 1.3, 7.2 Hz, 1H of Ph); 7.84–7.93 (2H, *m*, 2H of Ph); 8.04–8.10 (2H, *m*, H–C(3''), H–C(4")); 8.23–8.29 (1H, *m*, H–C(6")); 12.69 (1H, *br s*, HO–C(5')).

Anal. Calcd. for $C_{18}H_{17}N_3O_4$ (339.35): C, 63.71; H, 5.05; N, 12.38. Found: C, 63.45; H, 5.25; N, 11.99.

(*S*)-2-Hydroxy-3-[5-hydroxy-1-(6-phenylpyridazin-3-yl)-1*H*-pyrazol-4-yl]-1-pyropyl Benzoate (**24**).

This compound was prepared from 3-hydrazino-6-phenylpyridazine (**20**), heating for 3 hours, trituration with ethyl acetate. Yield: 0.133 g (32%), m.p. 179–182 °C (from ethyl acetate). $[\alpha]_D^{22}$ –14.7° (*c* = 0.30, DMF). IR(cm^{-1}): 3525 (OH), 1698 (C=O). ^{1}H nmr (dimethyl sulfoxide–d_6): δ 2.74 (1H, *dd*, *J* = 7.2, 15.6 Hz, H–C(3)); 2.81 (1H, *dd*, *J* = 5.5, 14.9 Hz, H–C(3)); 4.23–4.32 (1H, *m*, H–C(2)); 4.33–4.41 (1H, *m*, H–C(1)); 4.42–4.50 (1H, *m*, H–C(1)); 7.40–7.48 (2H, *m*, 2H of Ph); 7.51–7.60 (5H, *m*, 4H of Ph, H–C(3'))); 7.99–8.11 (5H, *m*, 4H of Ph, H–C(5")); 8.21 (1H, *br d*, *J* = 8.7 Hz; H–C(4")); 12.00 (1H, *br s*, HO–C(5')).

Anal. Calcd. for $C_{23}H_{20}N_4O_4$ (416.44): C, 66.34; H, 4.84; N, 13.45. Found: C, 65.90; H, 4.63; N, 13.02.

(*S*)-5-Benzoyloxymethyl-3-[(pyridin-2-yl)aminomethylidene]-tetrahydrofuran-2-one (**25**).

This compound was prepared from 2-aminopyridine (**21**), heating for 3 hours, trituration with ethyl acetate. Yield: 0.144 g (44%), m.p. 177–179 °C (from ethyl acetate). $[\alpha]_D^{22}$ +118° (*c* = 0.81, dichloromethane). IR(cm^{-1}): 3447 (OH), 1719 (C=O). ^{1}H nmr (dimethyl sulfoxide–d_6): δ 2.76 (1H, *ddd*, *J* = 2.3, 4.9, 16.2 Hz, H–C(4)); 3.09 (1H, *ddd*, *J* = 2.3, 9.0, 16.2 Hz, H–C(4)); 4.43 (1H, *dd*, *J* = 5.3, 13.5 Hz, H–C(5')); 4.50 (1H, *dd*, *J* = 3.4, 15.3 Hz, H–C(5')); 4.90–4.98 (1H, *m*, H–C(5)); 6.92–6.98 (2H, *m*, H–C(3"), H–C(5")); 7.50 (2H, *t*, *J* = 7.5 Hz, 2H of Ph); 7.65 (1H, *t*, *J* = 7.5 Hz, 1H of Ph); 7.70 (1H, *d*, *J* = 1.9 Hz, H–C(4")); 7.90–7.97 (2H, *m*, 2H of Ph); 8.24 (1H, *dd*, *J* = 3.4, 4.9 Hz, H–C(6")); 8.30 (1H, *tt*, *J* = 2.3, 10.2 Hz, H–C(3')); 9.68 (1H, *d*, HN–C(3')).

Anal. Calcd. for $C_{18}H_{16}N_2O_4$ (324.34): C, 66.66; H, 4.97; N, 8.64. Found: C, 66.53; H, 4.85; N, 8.63.

(*S*)-5-Benzoyloxymethyl-3-[(4,6-dimethylpyrimidin-2-yl)amino-methylidene]tetrahydrofuran-2-one (**26**).

This compound was prepared from 2-amino-4,6-dimethyl-pyrimidine (**22**), heating for 3 hours, trituration with dichloromethane/ethanol/diethyl ether. Yield: 0.158 g (45%), m.p. 90–92 °C (from dichloromethane/ethanol/diethyl ether). $[\alpha]_D^{22}$ +106.7° (*c* = 0.15, DMF). MS (EI): *m/z* = 353 (M^+). IR(cm^{-1}): 1754, 1720 (C=O). ^{1}H nmr (deuteriochloroform): δ 2.38 (6H, *s*, Me–(4'), Me–C(6')); 2.79 (1H, *ddd*, *J* = 2.3, 5.3, 16.2 Hz, H–C(4)); 3.12 (1H, *ddd*, *J* = 2.3, 8.7, 15.8 Hz, H–C(4)); 4.44 (1H, *dd*, *J* = 5.7, 12.1 Hz, H–C(5')); 4.56 (1H, *dd*, *J* = 3.5, 12.1 Hz, H–C(5')); 4.90–4.99 (1H, *m*, H–C(5)); 6.63 (1H, *s*, H–C(5")); 7.37–7.47 (2H, *m*, 2H of Ph); 7.55 (1H, *tt*, *J* = 1.3, 7.5 Hz, 1H of Ph); 7.98–8.07 (2H, *m*, 2H of Ph); 8.30 (1H, *br d*, *J* = 12.4 Hz, H–C(3')); 8.54 (1H, *dt*, *J* = 2.5, 12.4 Hz, HN–C(3')). ^{13}C nmr (deuteriochloroform): δ 24.1, 27.1, 66.5, 74.3, 99.5, 114.8, 128.8, 129.8, 130.2, 133.6, 134.4, 157.5, 166.6, 168.8, 172.4.

Anal. Calcd. for $C_{19}H_{19}N_3O_4$ (353.38) x H_2O: C, 61.45; H, 5.70; N, 11.31. Found: C, 61.79; H, 5.46; N, 10.19. HRMS Cald. for $C_{19}H_{19}N_3O_4$: 353.137556. Found: 353.138850.

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[11] The crude compound **3** is usually contaminated with up to 30% of ethyl (*S*)-tetrahydrofuran-5-carboxylate (**3'**), which is also the precursor of **4**. Reduction of either **3** or **3'** with $NaBH_4$, leads to the same product **4**, in both cases [9]. In the literature [9], the yield of **3** is not given.