Scientific paper

Enantioselective "Interrupted" Feist-Bénary Reaction Using Cinchona Ether Organocatalyst

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Received: 03-09-2008

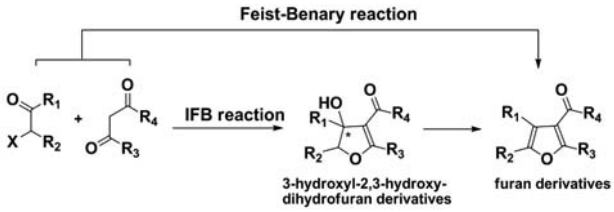
Abstract

The asymmetric "interrupted" Feist-Bénary (IFB) reaction of α-haloketones with β-dicarbonyl compounds was promoted by cinchona alkaloid ether derivatives, to give optically active dihydrofurans. Various ether derivatives as organocatalysts were examined. The corresponding chiral hydroxy dihydrofurans have been obtained in excellent yields and moderate *ee*s.

Keywords: Cinchona alkaloids; asymmetric catalysis; furan compounds; "Interrupted" Feist-Bénary reaction.

1. Introduction

The preparation of 2,3-dihydrofuran-containing molecules has been promising in organic synthesis as a result of their broad application to organic and medicinal chemistry.[1] The interrupted Feist-Bénary (IFB) reaction of α-haloketones with β-dicarbonyl compounds serves as a powerful synthetic method in this area of dihydrofuran chemistry.[2,3] To date reports of this reaction are sparse,[4] while an asymmetric version of this reaction would furnish enantiomerically enriched adducts. A great deal of effort has been directed toward the research of this reaction.



Scheme 1: IFB reaction

Recently, we have disclosed an organocatalytic enantioselective approach for the IFB reaction in high yields (91–98%) with up to 96% *ee*.[5,6,7] The ethers of 1,4-dichlorophthalazine and 3,6-dichloropyridazine were found to express good catalytic activities. Further research is needed to investigate the influence of bridge groups on the enantioselectivity. In this contribution, we wish to describe our investigation that has led to the development of an efficient method for carrying out enantioselective IFB reactions by using cinchona alkaloid ether derivatives. In addition, a family of chiral ether catalysts had been previously identified to catalyze enantioselective dihydroxylation reactions by Bradley[8] and Sharpless.[9] Intrigued by the possibility that these compounds might constitute an emerging class of privileged enantioselective catalysts, we investigated their activity in the asymmetric IFB reaction. Structures of organocatalysts are listed in Figure 1. Among them structures **2-6** represent new compounds.

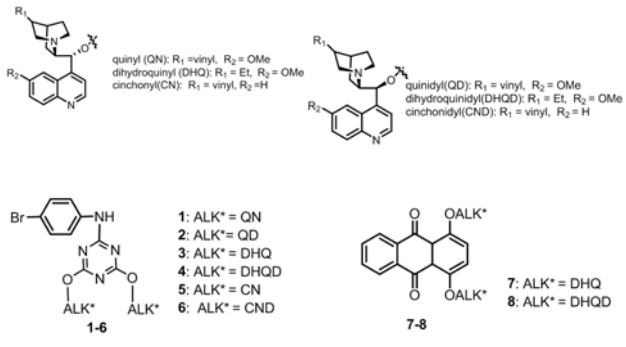


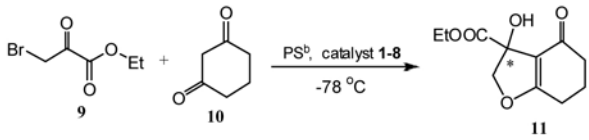
Figure 1: Structures of asymmetric IFB reaction catalysts

2. Results and Discussion

2. 1. Asymmetric "Interrupted" Feist-Bénary Reaction

To test their catalytic ability to promote asymmetric IFB reaction, a reaction between ethyl bromopyruvate **9** and 1,3-cyclohexadione **10** in the presence of 10 mol % of catalyst in THF at –78 °C was carried out. The results reveal that the organocatalyzed processes proceeded smoothly (10 min) in high yields (>90%). Among the organocatalysts probed, derivatives of quinine and quinidine displayed lower enantioselectivity than their dihydro analogues (entry 1, 3 vs. entry 2, 4). Additionally, the triazine bridge group was more beneficial for the chiral induction than that of anthraquinone.

Table 1: Yields and enantioselectivities of compound **11**, using different catalysts.[a]

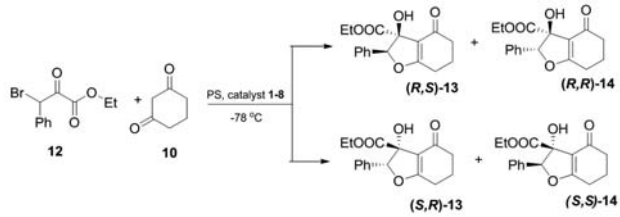


entry	catalyst	yield (%)[c]	*ee* (%)[d]
1	**1**	89	59(*S*)
2	**2**	95	70(*R*)
3	**3**	92	52(*S*)
4	**4**	94	68(*R*)
5	**5**	91	54(*R*)
6	**6**	94	34(*S*)
7	**7**	90	47(*S*)
8	**8**	89	52(*R*)

[a] Reactions were carried out using 10 mol % of catalyst at –78 °C in THF.
[b] PS, N,N,N',N'-tetramethyl-1,8-naphthalene-diamine.
[c] Isolated yield.
[d] Determined by HPLC analysis.

The catalytic activities of the β-substituted substrates were also tested (Table 2 and 3). Two stereogenic centers are formed in these reactions, leading to two pairs of enantiomers. With β-phenyl ethyl bromopyruvate **12** as the substrate, the two pairs of enantiomers (*R,S*)-**13**/(*S,R*)-**13** and (*R,R*)-**14**/(*S,S*)-**14** were obtained, and **13** was the main product (Table 2). In case of the CN and CND cinchona alkaloids, a drop in the *ee* was noticed (entry 5, 6), similarly to the previous IFB reaction result in Table **1**. With no oxygen-based substituent at position 6' in the quinoline ring, cinchona alkloids CN and CND were found to afford the desired adduct with lower enantioselectivities than those bearing a 6'-methoxyquinoline moiety. The substitution in the quinoline ring was characterized by spatial limitation, which is beneficial to the asymmmetric induction. As a whole, the asymmetric induction of the β-substituted substrate was better than that of the unsubstituted substrate.

Table 2. Yields and enantioselectivities of compounds **13** and **14**, using different catalysts.[a]

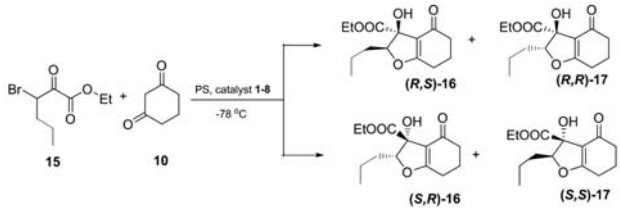


entry	catalyst	yield (13+14) (%)[b]	13:14[c]	*ee* (%)[d]
1	**1**	90	76:24	78
2	**2**	93	63:37	71
3	**3**	93	63:37	84
4	**4**	93	83:17	71
5	**5**	91	79:21	35
6	**6**	95	73:27	50
7	**7**	94	77:23	77
8	**8**	94	80:20	70

[a] The reactions were carried out using 10 mol % of catalysts at –78 °C in THF.
[b] Isolated yield.
[c,d] Determined by HPLC analysis.

Encouraged by these results, we next investigated β-propyl ethyl bromopyruvate **15**. In this case, the IFB reaction gave good yields; however, the obtained *ee*s were moderate (Table 3). Compared with the results in Table 2, a significant enhancement in diastereoselectivity was observed (> 95 : 5).

Table 3. Yields and enantioselectivities of compounds **16** and **17**, using different catalysts.[a]

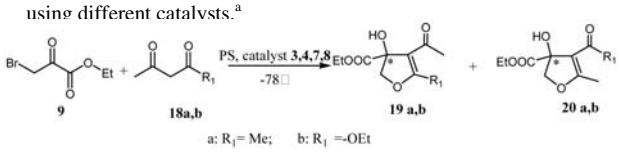


entry	catalyst	yield 16+17 (%)[b]	16:17[c]	*ee* (%)[d]
1	**1**	92	96:4	64
2	**2**	93	96:4	84
3	**3**	93	96:4	64
4	**4**	92	96:4	82
5	**5**	91	97:3	54
6	**6**	92	95:5	38
7	**7**	94	96:4	65
8	**8**	93	97:3	69

[a] The reactions were carried out using10 mol % of catalysts at –78 °C in THF.
[b] Isolated yield. [c,d] Determined by HPLC analysis.

To establish the generality of this reaction in substrate scope, we finally examined the IFB reaction between **9** and alicyclic β-dicarbonyl compounds (**18a,b**) in the presence of catalysts **3-4,** and **7-8** (Table 4). The desired product was isolated in satisfactory to good yields, accompanied by a sizable decrease in the *ee*. Even more disappointing were the results with **3**, which gave almost no *ee* at all (entry 1).

Table 4. Yields and enantioselectivities of compounds **19** and **20**, using different catalysts.[a]

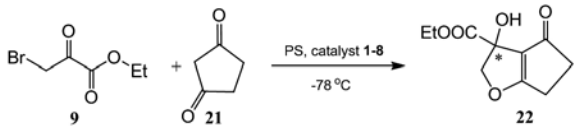


entry	starting material	catalyst	yield (%)[b]	19:20[c]	*ee*[d]
1	**18a**	**3**	83	–	2
2	**18a**	**4**	87	–	6
3	**18a**	**7**	90	–	11
4	**18a**	8	89	–	19
5	**18b**	**3**	82	89:11	21
6	**18b**	**4**	91	88:12	20
7	**18b**	**7**	87	93:7	19
8	**18b**	8	85	90:10	25

[a] The reactions were carried out using10 mol % of catalysts at –78 °C in THF.
[b] Isolated yield. [c,d] Determined by HPLC analysis.

Furthermore, the asymmetric IFB reaction of ethyl bromopyruvate **9** with 1,3-cyclopentanedione **21** was tested, but the enantioselectivities and yields were greatly disappointing.

Table 5. Yields and enantioselectivities of compound **22**, using different catalysts.[a]



entry	catalyst	yield (%)[b]	*ee* (%)[c]
1	**1**	73	11(*S*)
2	**2**	82	6(*R*)
3	**3**	80	8(*S*)
4	**4**	81	15(*R*)
5	**5**	73	12(*R*)
6	**6**	80	7(*S*)
7	**7**	81	9(*S*)
8	**8**	75	2(*R*)

[a] The reactions were carried out using10 mol % of catalysts at –78 °C in THF.
[b] Isolated yield.
[c] Determined by HPLC analysis.

3. Conclusion

In summary, we have developed an enantioselectivtive organocatalyzed IFB reaction of ethyl bromopyruvate with 1,3-dione in THF, by using a variety of cinchona alkaloid ether derivatives as catalysts. This newly introduced catalysts will complement the very few examples of organocatalyzed IFB reactions reported to date (Table **1-4**). All reactions went smoothly to give products in moderate to excellent yields and enantioselectivities. Further investigations of new organocatalysts in this reaction and its applications to the synthesis of biologically active molecules are underway and will be reported in due course.

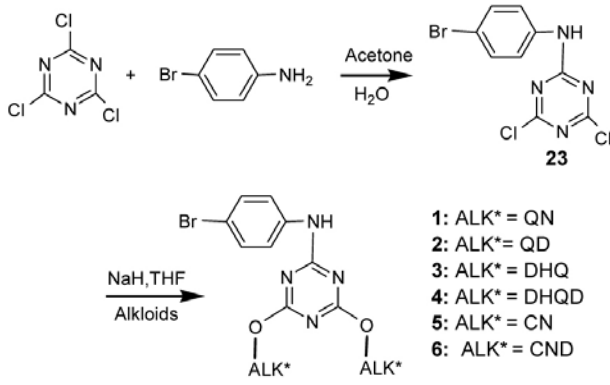
4. Experimental Section

4. 1. Materials and Apparatus

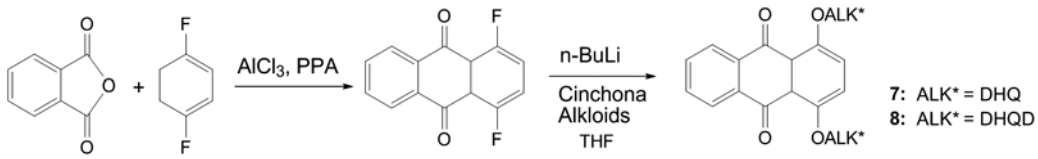
Chemicals were used as purchased, and NMR spectra were measured on a 300 MHz Bruker Avance 300 DPX spectrometer. Chemical shifts (ppm) are reported relative to the tetramethylsilane. Mass spectra were recorded on a MICROMASS Quattro Premier Spectrometer. High performance liquid chromatography (HPLC) was performed by an Agilent 1100 chromatograph interfaced to an HP 71 series computer workstation with a Daicel Chiralpak OD, OJ or AD chiral column. 3-bromo-2-ketoesters were synthesized by literature procedures.[10,11]

4. 2. Experimental Procedures

General synthesis of orgnocatalyst 1-6: A solution of cyanuric chloride (10.0 g, 54 mmol) in acetone (100 mL) was heated to 50 °C and added to stirred crushed ice/water (200 mL). 4-bromoaniline (18.7 g, 10.8 mmol) dissolved in an acetone/water mixture (1:1, 100 mL) was added dropwise to the above solution with vigorous stirring. After stirring at 0 °C for 2 h, the resulting yellow suspension was filtered, washed with cold water (20 mL) and dried to yield **23** as a pale solid (17.1 g, 3.9 mmol).



Scheme 3. The synthesis of organocatalysts **1-6**



Scheme 4. The synthesis of organocatalysts **7-8**.

Preparation of 3 as example: Compound **23** (17.1 g, 53.9 mmol) was dissolved in dry THF (50 mL) and added to a stirred suspension of dihydroquinine (36.6 g, 54 mmol) and NaH (60%) (6.5 g, 0.17 mol) in THF (200 mL). The reaction mixture was refluxed overnight and then quenched by adding saturated NH_4Cl solution (100 mL). The phases were separated, the product extracted into ethyl acetate (3 × 200 mL) and the solvent removed in vacuo to afford a white solid, which was chromatographed (EtOAc/Ethanol/NEt_3, 7/3/0.5) to give **3** as a white solid.

Synthesis of organocatalyst 7-8: They were easily prepared by nuclephilic sbstitution of 1,4-difluoroanthraquinone with lithium salt of dihydroquinidine or dihydroquinine in THF at room temperature.[9] All analytical data were identical to those reported.[9]

Asymmetric IFB reaction of ethyl bromopyruvate with cyclic 1,3-dione: 1,3-cyclohexadione (1,3-cyclopentanedione) (0.40 mmol), proton sponge (PS, N,N,N',N'-tetramethyl-1,8-naphthalenediamine, 85 mg, 0.40 mmol) and organocatalyst (0.04 mmol) were dissolved in THF (4 mL) and cooled to –78 °C. Ethyl bromopyruvate (50 μL, 0.40 mmol) was then added dropwise, and the solution allowed to stir for 10 min. The reaction mixture was warmed to room temperature, concentrated, and purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 50/1).

Asymmetric IFB reaction of ethyl bromopyruvate with acyclic 1,3-dione: Acetylacetone (0.40 mmol), proton sponge (86 mg, 0.40 mmol), and catalyst (0.04 mmol) were dissolved in THF (4 ml) and cooled to –78 °C. Ethyl bromopyruvate (50 μL, 0.40 mmol) was then added dropwise, and the solution was allowed to stir for 10 min. The reaction mixture was warmed to room temperature, concentrated, and purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 100/1).

Asymmetric IFB reaction of β-substituted ethyl bromopyruvate with 1,3-cyclohexadione: 1,3-cyclohexadione (44.8 mg, 0.40 mmol), proton sponge (85 mg, 0.40 mmol), TBABr (64 mg, 0.20 mmol) and organocatalyst (0.04 mmol) were dissolved in THF (4 mL) and cooled to –78 °C. The appropriate 3-bromo-2-ketoester (50 μL, 0.40 mmol) was added dropwise, and the solution allowed to stir for 10 min. The reaction mixture was warmed to room temperature, concentrated, and purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 100/1).

5. Acknowledgments

We thank the National Natural Science Foundation of China (Nos. 20572131, 20372083, 20302014).

6. References

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Povzetek

Prispevek poroča o pripravi optično aktivnih dihidrofuranov s pomočjo izboljšane asimetrične »prekinjene (interrupted) Fiest-Bénary (IFB) reakcije α-haloketonov z β-dikarbonilnimi spojinami z uporabo različnih etrskih derivatov kinolinskih alkaloidov kot katalizatorjev. Ustrezni kiralni hidroksi dihidrofurani so bili pripravljeni z odličnimi izkoristki in solidnimi enantiomernimi preseški (*ee*).

Products characterizations:

Compound 1, [α] = +160.2 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ0.90–1.50 (m,8H), 1.77–2.27 (m, 6H), 2.73–3.23 (m, 12H), 3.89 (s, 6H), 5.10 (m, 4H), 6.08 (m, 2H), 6.63 (m, 2H), 6.80 (m, 2H), 6.90 (m, 2H), 7.40 (b, 2H), 7.73 (b, 1H), 8.03 (d,J = 9.1 Hz, 2H), 8.68 (s, 2H), ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 172.4, 166.2, 157.8, 147.4, 144.5, 143.6, 140.4, 136.1, 131.7, 131.4, 126.5, 122.7, 121.4, 116.8, 115.0, 101.9, 59.1, 55.7, 49.3, 40.1, 28.3, 26.3; IR(KBr) (ν cm^{-1}) 3398, 2939, 1620, 1596, 1571, 1533, 1508, 1488, 1406, 1353, 1228, 1134; MS for $C_{49}H_{51}BrN_8O_4$: *m/z* 895.8 (M + H^+). All analytical data were identical to those reported.[8]

Compound 2, $[\alpha]_D^{20}$ = –98.4 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ1.48–0.95 (m,8H), 1.78–2.15 (m, 6H), 2.63–3.35 (m, 12H), 3.90 (s, 6H), 5.12 (m, 4H), 6.08 (m, 2H), 6.59 (m, 2H), 6.81 (m, 2H), 6.79 (m, 2H), 7.41 (b, 2H), 7.72 (b, 1H), 8.02 (d, J = 9.1 Hz, 2H), 8.67 (s, 2H), ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.5, 166.0, 157.9, 147.4, 144.5, 143.6, 140.4, 136.2, 131.8, 131.4, 126.6, 122.7, 121.5, 116.8, 115.0, 101.9, 59.2, 55.7, 49.3, 40.1, 28.3, 26.4; IR(KBr) (ν cm^{-1}) 3404, 2935, 2871, 1620, 1596, 1566, 1508, 1458, 1406, 1352, 1228, 1134; MS for $C_{49}H_{51}BrN_8O_4$: *m/z* 895.8 (M + H^+).

Compound 3, $[\alpha]_D^{20}$ = +179.7 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ1.08 (m, 6H), 1.07 (t,J = 7.2 Hz, 2H), 1.26 (m, 4H), 1.45 (m, 4H), 1.81 (s,6H), 3.20–3.36 (m, 8H), 2.59–2.65 (m, 4H), 3.05–3.33 (m, 6H), 3.93 (d,J = 2.4 Hz, 2H), 6.66 (s, 2H), 6.72 (m, 2H), 6.83 (d,J = 9.6 Hz, 2H), 7.43 (m, 2H), 7.56 (b, 1H), 8.05(d,J = 11.2 Hz, 2H), 8.66 (s, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 165.9, 158.1, 147.5, 144.5, 143.6, 135.9, 131.9, 131.5, 122.6, 121.6, 118.4, 116.9, 101.8, 59.2, 58.7, 55.8, 46.2, 43.3, 37.5, 28.1, 27.6, 25.5, 25.4, 12.1; IR(KBr) (ν cm^{-1}) 3419, 2929, 2869, 1622, 1598, 1562, 1508, 1488, 1402, 1350, 1242, 1230, 1134; MS for $C_{49}H_{55}BrN_8O_4$: *m/z* 899.2 (M + H^+).

Compound 4, $[\alpha]_D^{20}$ = –101.3 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ1.08 (m, 6H), 1.07 (t,J = 7.2 Hz, 2H), 1.28 (m, 4H), 1.43 (m, 4H), 1.78 (s,6H), 3.25–3.38(m,8H), 2.59–2.65 (m, 4H), 3.05–3.33 (m, 6H), 3.93 (d,J = 2.4 Hz, 2H), 6.59 (s, 2H), 6.72 (m, 2H), 6.79 (d, J = 9.6 Hz, 2H), 7.41 (m, 2H), 7.55 (b, 1H), 8.03 (d,J = 11.2 Hz, 2H), 8.65 (s, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.6, 165.9, 157.9, 147.5, 144.6, 143.7, 136.1, 131.9, 131.5, 126.7, 122.6, 121.5, 116.9, 102.0, 59.5, 55.7, 51.0, 50.2, 37.4, 27.1, 25.9, 25.2, 21.8, 12.0; IR(KBr) (ν cm^{-1}) 3413, 2933, 2871, 1620, 1596, 1569, 1558, 1539, 1508, 1458, 1406, 1350, 1228,1134; MS for $C_{49}H_{55}BrN_8O_4$: *m/z* 899.2 (M + H^+).

Compound 5, $[\alpha]_D^{20}$ = +2.3 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ1.09–1.78 (m, 10H), 2.02 (s, 2H), 2.42–2.78 (m,6H), 3.21–3.50 (m,6H), 4.93 (m, 4H), 5.75 (m, 2H), 6.67 (d,J = 8.0 Hz, 4H), 6.28 (d,J = 8.0 Hz, 2H), 7.61 (s, 2H), 7.78 (m, 2H), 8.13 (d,J = 7.2 Hz, 4H), 8.77 (s, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.4, 166.0, 150.1, 148.4, 140.5, 136.0, 131.5, 130.5, 129.2, 126.7, 123.5, 122.8, 117.0, 114.9, 59.9, 59.8, 50.2, 49.3, 41.2, 40.0, 37.4, 28.2, 26.4, 12.2; 3421, 2933, 1596, 1560, 1488, 1456, 1400, 1148, 1132; MS for $C_{47}H_{47}BrN_8O_2$: *m/z* 835.8 (M + H^+).

Compound 6, $[\alpha]_D^{20}$ = +71.1 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ1.15–1.83 (m, 10H), 2.26 (s, 2H), 2.62–2.81 (m, 6H), 3.26–3.46 (m,6H), 4.94 (m, 4H), 5.71 (m, 2H), 6.70 (d,J = 8.0 Hz, 4H), 6.29 (d,J = 8.0 Hz, 2H), 7.60 (s, 2H), 7.74 (m, 2H), 8.14 (d,J = 7.2 Hz, 4H), 8.77 (s, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.4, 165.9, 150.0, 148.4, 145.3, 141.5, 136.0, 131.4, 130.5, 129.3, 126.9, 125.6, 123.4, 122.7, 117.0, 114.5, 59.9, 58.9, 42.9, 39.7, 27.7, 27.5; IR(KBr) (ν cm^{-1}) 3404, 2937, 2864, 1598, 1560, 1541, 1488, 1456, 1394, 1346, 1132, 813, 757; MS for $C_{47}H_{47}BrN_8O_2$: *m/z* 835.8 (M + H^+).

Compound 7, m.p. 177–180 °C ; $[\alpha]^{20}$, D = +579 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ0.80 (t, J = 7.3 Hz, 6H), 1.14–1.44 (m. 8H), 1.59 (brs, 2H), 1.92 (brs, 2H), 2.05 (brs, 2H), 2.35–2.61(m, 6H), 3.05(dd, J = /3.4, 10.0 Hz, 2H), 3.23(brs, 4H), 3.92 (s, 6H), 5.95 (brs, 2H), 6.61 (brs, 2H), 7.32 (brs, 2H), 7.37 (dd. J = 9.2, 1.5 Hz, ZH), 7.43(d, J = 4.5 Hz, 2H), 7.79(dd, J = 5.7, 3.3 Hz, 2H), 8.03(d, J = 9.2 Hz, 2H), 8.28(dd, J = 5.7, 3.3 Hz, 2H), 8.64 (d, J = 4.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.1, 20.9, 25.6, 27.7, 37.8, 37.6, 43.5, 55.8, 58.9, 60.0, 804 (br), 100.6(br), 118.7, 120.6, 122.0, 123.4, 126.2, 126.4, 132.1, 133.3, 134.3, 142.8, 144.6, 147.6, 151.0, 158.2. 182.7; IR(KBr) (ν cm^{-1}) 2954, 2931, 2871, 1669, 1621, 1509, 1461, 1262, 1243, 1005; MS for $C_{54}H_{56}O_6N_4$: *m/z* 845.3 (M + H^+).

Compound 8, m.p. 152–157 °C; $[\alpha]^{20}$ D = – 487 (*c* 1.0, $CHCl_3$);^1H NMR (300 MHz, $CDCl_3$) δ0.84(t, J = 7.3, 6H), 1.25–1.77(m, 14H), 2.41(brs, 2H), 2.40–2.81 (m, 8H), 3.24(2H), 3.92(s, 6H), 5.87(brs, 2H), 6.65(s, 2H), 7.36(dd, J = 9.4, 2.2 Hz, 4H), 7.49 (d, J = 4.2 Hz, 2H), 7.79(dd, J = 5.7, 3.3 Hz, 2H), 8.02(d, J = 9.4 Hz, 2H), (dd, J = 5.8, 3.3 Hz, 2H), 8.65 (d. J = 4 5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.1, 24.5, 26.5, 27.2, 37.8, 50.2, 51.0, 55.7, 60.3, 81.0, 100.7, 119.l, 120.4, 127.0, 123.4, 126.2, 126.5, 132.0, 133.3, 134.3, 143.0, 144.6, 147.6, 151.2, 158.0, 182.9; IR(KBr) (ν cm^{-1}) 2934, 2871, 1669, 1620, 1508, 1463, 1260, 1243, 1030; MS for $C_{54}H_{56}O_6N_4$: *m/z* 845.4 (M + H^+).

3-hydroxy-4-oxo-hexahydrobenzofuran-3-carboxylic acid ethyl ester (11). ^1H NMR ($CDCl_3$, 300 MHz) δ1.29 (t, *J* = 6.0 Hz, 3H), 2.10 (d, *J* = 4.2 Hz, 2H), 2.35 (q, *J* = 4.8 Hz, 2H), 2.55 (t, *J* = 6.0 Hz, 2H), 3.50 (s, OH), 4.31 (q, *J* = 6.9 Hz, 3H), 4.51 (d, *J* = 10.5 Hz, 1H), 4.73 (d, *J* = 10.5 Hz, 1H); Enantiomers separated and quantified by analytical HPLC (Daicel Chiralpak OD, he-

xane:*i*-propanol 94:6, 0. 5 mL/min, 257 nm), t_R = 37.9 min, 49.6 min.

3-hydroxy-2-phenyl-4-oxo-hexahydrobenzofuran-3-carboxylic acid ethyl ester (13). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.34 (t, *J* = 7.2 Hz, 3H), 2.14 (t, *J* = 6.3 Hz, 2H), 2.40 (q, *J* = 5.1 Hz, 2H), 2.66 (t, *J* = 6.3 Hz, 2H), 4.37 (q, *J* = 7.0 Hz, 2H), 5.78 (s, 1H), 7.24–7.39 (m, 5H); Enantiomers separated and quantified by analytical HPLC (Daicel Chiralpak AD, hexane:*i*-propanol 85:15, 0.5 mL/min, 259nm), $t_{R(2S,3S)}$ = 43.9 min, $t_{R\ (2R,3R)}$ = 59.4 min.

3-hydroxy-2-propyl-4-oxo-hexahydrobenzofuran-3-carboxylic acid ethyl ester(16). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96 (t, *J* = 7.5 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.48–1.39 (m, 2H), 1.85–1.75 (m, 2H), 2.11–2.05 (m, 2H), 2.36–2.31 (m, 2H), 2.51 (t, *J* = 5.4 Hz, 2H), 3.77 (s, OH), 4.34–4.23 (q, *J* = 6.9 Hz, 2H), 4.72 (t, *J* = 6.9 Hz, 1H); Enantiomers separated and quantified by analytical HPLC (Daicel Chiralpak AD, hexane: *i*-propanol = 90:10, 0.5 mL/min, 257 nm), $t_{R\ (2R,3R)}$ = 52.4 min, $t_{R\ (2S,3S)}$ = 60.7 min.

3-Hydroxyl-4-acetyl-5-methyl-hydrofuran-3-carboxylic acid ethyl ester (19a). ^{1}H NMR ($CDCl_3$, 300MHz): 1.22–1.33 (m, 6H), 2.35 (s, 3H), 4.28 (q, J = 7.2 Hz, 2H), 4.37 (d, J = 10.5 Hz, 1H), 4.50 (d, J = 10.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5MHz) : d 193.2, 173.5, 171.6, 118.8, 83.3, 80.5, 62.8, 28.8, 15.7, 14.1; HRMS: *m/z*: 212.9 (M + H^+). Enantiomers separated and quantified by analytical HPLC (Daicel Chiralpak OD-H, hexane:*i*-propanol 97:3, 0.5 ml/min, 257 nm); t_R = 44.32, 53.26 min.

3-Hydroxy-4-acetyl-5-ethoxy-hydrofuran-3-carboxylic acid ethyl ester (19b). ^{1}HNMR ($CDCl_3$, 300 MHz): 1.22–1.31 (m, 6H), 2.30 (s, 3H), 4.26 (q, J = 7.2 Hz, 2H), 4.29 (q, J = 7.2 Hz, 2H), 4.41 (d, J = 10.5 Hz, 1H), 4.56 (d, J = 10.5 Hz, 1H); ^{13}C NMR($CDCl_3$, 75.5 MHz): 194.1, 173.3, 164.2, 82.6, 80.7, 79.1, 62.7, 59.7, 29.7, 14.5, 14.0; HRMS: *m/z*: 245.2 (M + H^+). Enantiomers separated and quantified by analytical HPLC (Daicel Chiralpak OD-H, hexane:*i*-propanol = 97:3, 0.5ml/min, 257 nm); t_R = 20.4, 22.0 min .

3-hydroxy-4-oxo-3,4,5,6-tetrahydro-2H-cyclopentafuran-3-carboxylic acid ethyl ester (22): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, J = 6.0 Hz, 3H), 2.60 (t, J = 6.3 Hz, 2H), 2.96 (t, J = 6.3 Hz, 2H), 3.50 (s, OH), 4.26 (q, J = 7.2 Hz, 3H), 4.90 (d, J = 9.9 Hz, 1H), 5.25 (d, J = 9.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 198.7, 194.3, 171.5, 123.3, 92.1, 83.2, 40.8, 29.7, 22.4, 14.1. Enantiomers separated and quantified by analytical HPLC (Daicel Chiralpak OJ–H, hexane:*i*-propanol 95:5, 0.5 mL/min, 257 nm), t_R = 45.1 min, 48.5 min.