

SYNTHESIS OF 3-(2-OXO-2H-PYRANYL-3) SUBSTITUTED LACTIC ACID DERIVATIVES

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Dedicated to Professor Teruaki Mukaiyama, Science University of Tokyo, on the occasion of his 73rd birthday

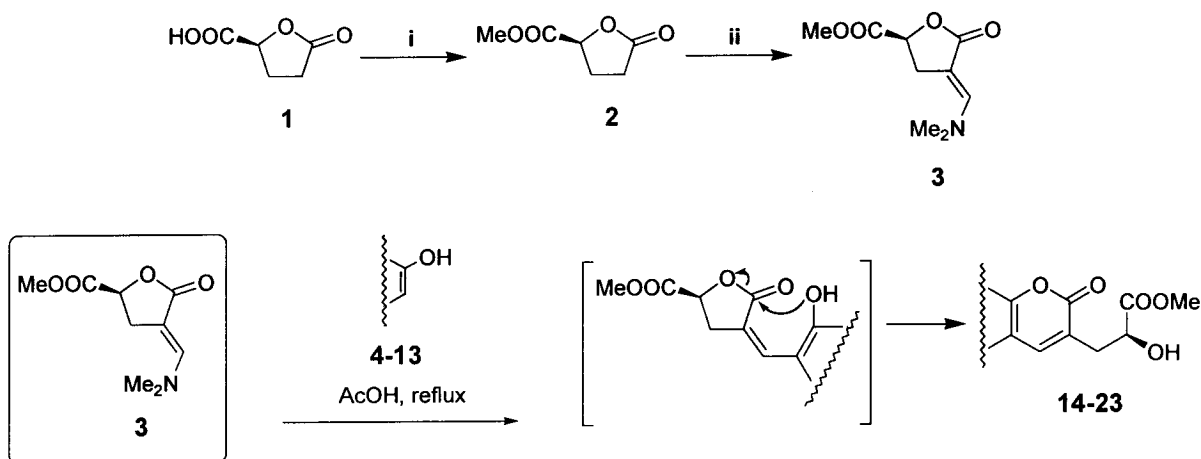
Abstract – (*S*)-3-[(*E*)-Dimethylaminomethylidene]-5-(methoxycarbonyl)tetrahydrofuran-2-one (**3**) was transformed in one step with various *C,O*-dinucleophiles (**4-13**) into the corresponding 3-(2-oxo-2*H*-pyranyl-3)-2-hydroxypropanoates (**14-23**).

Chiral hydroxy acids, such as lactic acid, malic acid, mandelic acid, tartaric acid, and their derivatives found a wide applicability in asymmetric synthesis, especially as chiral synthons, chiral auxiliaries, and resolving agents.¹ However, much less attention has been paid to the synthesis and utilisation of heteroaryl substituted α -hydroxy acid derivatives. Previously, we have shown that 3-dimethylaminopropenoates can serve as versatile reagents for the preparation of a variety of heterocyclic systems.^{2,3} In this connection we have recently shown the utilisation of chiral 3-dimethylaminopropenoate analogs, derived from L-pyroglutamic acid, for the preparation of 3-heteroarylalanine derivatives and heterocyclic systems with an α -amino acid structural element.⁴⁻⁶ In continuation of our work in this field, we now report on novel, one step synthesis of methyl 3-(2-oxo-2*H*-pyranyl-3)-2-hydroxypropanoates (**14-23**) from easily available (*S*)-3-[(*E*)-dimethylaminomethylidene]-5-(methoxycarbonyl)tetrahydrofuran-2-one (**3**).⁶

The starting compound, (*S*)-3-[(*E*)-dimethylaminomethylidene]-5-(methoxycarbonyl)tetrahydrofuran-2-one (**3**), was prepared from commercially available (*S*)-5-oxotetrahydrofuran-2-carboxylic acid (**1**).⁶ When compound (**3**) was treated with carbocyclic and heterocyclic 1,3-dicarbonyl compounds and their analogs (**4-13**), the corresponding methyl 3-heteroaryl-2-hydroxypropanoates (**14-23**) with fused 2*H*-pyran-2-one heterocyclic residue were formed (Scheme 1).

The following 1,3 dicarbonyl compounds and their analogs were chosen: cyclohexane-1,3-dione (**4**), 5,5-dimethylcyclohexane-1,3-dione (**5**), 1,5-dihydroxynaphthalene (**6**), 2,3-dihydroxynaphthalene (**7**), 2,7-

Scheme 1



Reagents and conditions: i MeOH, SOCl_2 ; ii $(\text{Me}_2\text{N})_2\text{CHO}-t\text{-Bu}$, toluene, 100° .

dihydroxynaphthalene (8), 1,3,5-trihydroxybenzene (9), 4-hydroxypyridin-2-one (10), 4-hydroxy-6-methyl-2H-pyran-2-one (11), 4-hydroxy-2H-benzo[b]pyran-2-one (12) and 1,3-dimethylbarbituric acid (13).

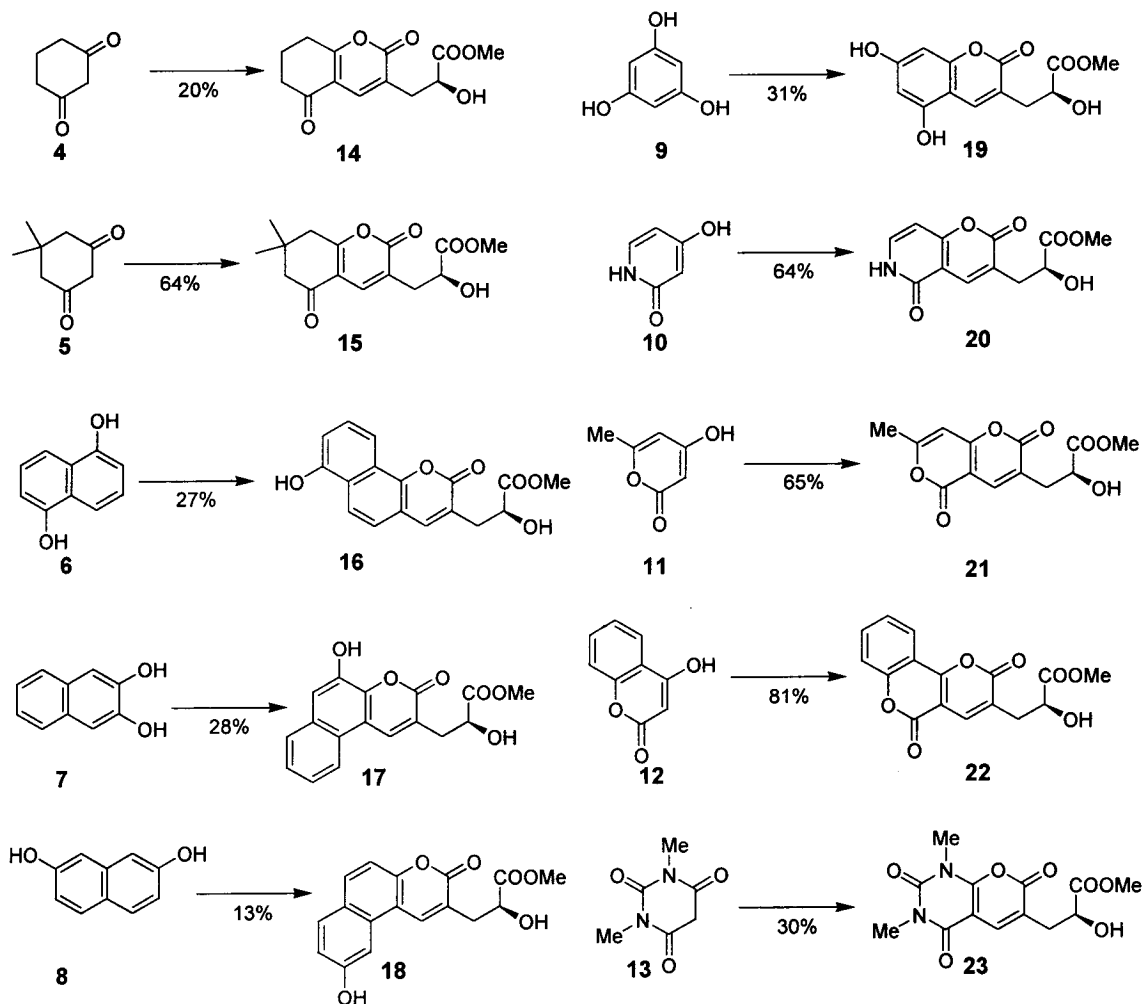
Compounds (4-13) gave after treatment with 3 in refluxing acetic acid, the corresponding methyl (S)-3-heteroaryl-2-hydroxypropanoates with the following heteroaryl residues: 2,5-dioxo-5,6,7,8-tetrahydro-2H-benzo[b]pyran-3 (14), 7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydro-2H-benzo[b]pyran-3 (15), 7-hydroxy-2-oxo-2H-naphtho[1,2-b]pyran-3 (16), 10-hydroxy-2-oxo-2H-naphtho[2,1-b]pyran-3 (17), 6-hydroxy-2-oxo-2H-naphtho[2,1-b]pyran-3 (18), 5,7-dihydroxy-2-oxo-2H-benzo[b]pyran-3 (19), 2,5-dioxo-5,6-dihydro-2H-pyrano[3,2-c]pyridin-3 (20), 2,5-dioxo-7-methyl-2H,5H-pyrano[4,3-b]pyran-3 (21), 2,5-dioxo-2H,5H-benzo[b]pyrano[4,3-b]pyran-3 (22), and 1,3-dimethyl-2,4,7-trioxo-1,2,3,4-tetrahydro-7H-pyrano[2,3-d]pyrimidin-6 (23), respectively (Scheme 2).

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^1H NMR spectra and ^{13}C NMR spectra were obtained on a Bruker Avance DPX 300 (300 MHz) spectrometer with $\text{DMSO}-d_6$ and CDCl_3 as solvents and Me_4Si as internal standard. The microanalyses for C, H, and N were obtained on a Perkin-Elmer CHN Analyser 2400. The optical rotations were measured on a Perkin-Elmer 241 MC Polarimeter.

(S)-5-(Methoxycarbonyl)tetrahydrofuran-2-one (2) and (S)-3-[(E)-dimethylaminomethylidene]-5-(methoxycarbonyl)tetrahydrofuran-2-one (1) were prepared according to the procedures described in the literature.^{6,7}

Scheme 2



(*S*)-3-[(*E*)-Dimethylaminomethylidene]-5-(methoxycarbonyl)tetrahydrofuran-2-one (**3**).⁶ A mixture of (*S*)-5-(methoxycarbonyl)tetrahydrofuran-2-one (**2**) (1.441 g, 10 mmol), toluene (20 ml), and bis(dimethylamino)-*tert*-butoxymethane (2.61 g, 15 mmol) was heated at 90–100°C for 2 h, volatile components were evaporated *in vacuo*, and the solid residue was crystallised from ethyl acetate. The precipitate was collected by filtration to give **3**; yield: 1.154 g, 58%; mp 113–115°C (from ethyl acetate); $[\alpha]_D^{23} = +2.3^\circ$ ($c = 1.10$, CH_2Cl_2). $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 3.04 (6H, s, NMe_2), 3.20 (1H, ddd, $J = 1.3, 4.7, 14.3$ Hz, 4-Ha), 3.43 (1H, ddd, $J = 1.1, 10.0, 14.1$ Hz, 4-Hb), 3.79 (3H, s, OMe), 4.86 (1H, dd, $J = 5.0, 10.0$ Hz, 5-H), 7.13 (1H, t, $J = 1.5$ Hz, 3'-H). $^{13}\text{C NMR}$ (75.5 MHz, CDCl_3): δ 30.2, 42.1, 52.8, 72.6, 84.8, 148.4, 171.8, 174.2. *Anal.* Calcd for $\text{C}_9\text{H}_{13}\text{NO}_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.31; H, 6.79; N, 7.14.

General Procedure for the Preparation of Fused 2*H*-Pyran-2-one Hydroxypropanoates (13-24):

A mixture of (*S*)-3-[(*E*)-dimethylaminomethylidene]-5-(methoxycarbonyl)tetrahydrofuran-2-one (**3**) (0.199 g, 1 mmol), 1,3-dinucleophile (**4-13**) (1 mmol), and glacial acetic acid (4 mL) was heated at reflux temperature for 2–5 h. Volatile components were evaporated *in vacuo*, the solid residue was crystallised from the appropriate solvent and the precipitate was collected by filtration to give substituted lactic acid derivatives (**14-23**).

Methyl (*S*)-3-(2,5-Dioxo-5,6,7,8-tetrahydro-2*H*-benzo[*b*]pyranyl-3)-2-hydroxypropanoate (14). This compound was prepared from cyclohexane-1,3-dione (**4**), reflux for 2 h; the crude product was purified by column chromatography using ethyl acetate/*n*-hexane (10 : 1) as solvent to give **14**; yield 20%; mp 122–124°C (from ethyl acetate/ether = 1 : 1); $[\alpha]_{\text{D}}^{23} = +25.5^\circ$ ($c = 1.00$, CH₂Cl₂). ¹H NMR (300 MHz, DMSO-*d*₆): δ 2.06 (2H, deg. tt, $J = 6.0$ Hz, 7-CH₂), 2.48 (2H, t, $J = 6.0$ Hz, 8-CH₂) 2.62 (1H, dd, $J = 8.7, 14.3$ Hz, 3-Ha), 2.82 (1H, dd, $J = 4.5, 14.0$ Hz, 3-Hb), 2.85 (2H, t, $J = 6.0$ Hz, 6-CH₂), 3.64 (3H, s, OMe), 4.28 (1H, ddd, $J = 4.7, 8.7, 6.2$ Hz, 2-H), 5.59 (1H, d, $J = 6.4$ Hz, OH), 7.65 (1H, s, 4'-H). ¹³C NMR (75.5 MHz, DMSO-*d*₆): δ 20.7, 28.0, 35.7, 36.9, 52.4, 68.7, 114.7, 122.6, 138.2, 161.6, 174.3, 174.4, 195.0. *Anal.* Calcd for C₁₃H₁₄O₆: C, 58.65; H, 5.30. Found: C, 58.47; H, 5.29.

Methyl (*S*)-3-(7,7-Dimethyl-2,5-dioxo-5,6,7,8-tetrahydro-2*H*-benzo[*b*]pyranyl-3)-2-hydroxypropanoate (15). This compound was prepared from 5,5-dimethylcyclohexane-1,3-dione (**5**), reflux for 3 h; yield 64%; mp 109–111°C (from ethyl acetate); $[\alpha]_{\text{D}}^{23} = -2.2^\circ$ ($c = 1.16$, CHCl₃). ¹H NMR (300 MHz, DMSO-*d*₆): δ 1.05 (6H, s, 7-Me), 2.41 (2H, s, CH₂), 2.62 (1H, dd, $J = 8.7, 13.9$ Hz, 3-Ha), 2.80 (2H, s, CH₂), 2.82 (1H, dd, $J = 4.4, 14.3$ Hz, 3-Hb), 3.63 (3H, s, OMe), 4.29 (1H, ddd, $J = 4.5, 8.7, 6.4$ Hz, 2-H), 5.60 (1H, d, $J = 6.4$ Hz, OH), 7.64 (1H, s, 4'-H). ¹³C NMR (75.5 MHz, DMSO-*d*₆): δ 27.5, 27.6, 32.3, 34.8, 49.7, 51.5, 67.8, 112.9, 121.7, 137.0, 161.0, 171.8, 173.5, 194.0. *Anal.* Calcd for C₁₅H₁₈O₆: C, 61.22; H, 6.16. Found: C, 60.92; H, 6.50.

Methyl (*S*)-3-(7-Hydroxy-2-oxo-2*H*-naphtho[1,2-*b*]pyranyl-3)-2-hydroxypropanoate (16). This compound was prepared from 1,5-dihydroxynaphthalene (**6**), reflux for 6 h; the crude product was purified by column chromatography using ether as solvent to give **16**; yield 27%; mp 171–173°C (from ethyl acetate); $[\alpha]_{\text{D}}^{23} = -39.5^\circ$ ($c = 1.16$, DMF). ¹H NMR (300 MHz, DMSO-*d*₆): δ 2.77 (1H, dd, $J = 9.0, 13.7$ Hz, 3-Ha), 2.97 (1H, dd, $J = 4.7, 13.8$ Hz, 3-Hb), 3.66 (3H, s, OMe), 4.43 (1H, dt, $J = 5.3, 7.9$ Hz, 2-H), 5.68 (1H, d, $J = 6.0$ Hz, 2-OH), 7.06 (1H, d, $J = 7.9$ Hz, 8'-H), 7.50 (1H, t, $J = 7.9$ Hz, 9'-H), 7.61 (1H, d, $J = 7.7$ Hz, 10'-H), 7.79 (1H, d, $J = 8.3$ Hz, 6'-H), 8.01 (1H, s, 4'-H), 8.02 (1H, d, $J = 8.3$ Hz, 5'-H), 10.48 (1H, br

s, 7'-OH). ^{13}C NMR (75.5 MHz, DMSO- d_6): δ 36.5, 52.4, 68.9, 111.7, 112.4, 115.8, 119.3, 123.4, 124.3, 124.9, 125.9, 128.9, 143.4, 150.1, 154.4, 161.8, 174.5. *Anal.* Calcd for $\text{C}_{17}\text{H}_{14}\text{O}_6$: C, 64.97; H, 4.49. Found: C, 64.57; H, 4.79.

Methyl (S)-3-(10-Hydroxy-2-oxo-2H-naphtho[2,1-b]pyranyl-3)-2-hydroxypropanoate (17). This compound was prepared from 2,3-dihydroxynaphthalene (7), reflux for 6 h; the crude product was purified by column chromatography using ether as solvent to give 17; yield 28%; mp 192–195°C (from ethyl acetate); $[\alpha]_{\text{D}}^{23} = -8.0^\circ$ ($c = 0.99$, CHCl_3). ^1H NMR (300 MHz, DMSO- d_6): δ 2.85 (1H, dd, $J = 8.7, 13.9$ Hz, 3-Ha), 3.03 (1H, dd, $J = 4.9, 13.6$ Hz, 3-Hb), 3.65 (3H, s, OMe), 4.48 (1H, dd, $J = 4.9, 8.7$ Hz, 2-H), 5.65 (1H, br s, 2-OH), 7.44 (1H, s, 9'-H), 7.47-7.54 (2H, m, 6'-H and 7'-H), 7.80-7.84 (1H, m, 8'-H), 8.35-8.38 (1H, m, 5'-H), 8.73 (1H, s, 4'-H), 10.45 (1H, br s, 10'-OH). ^{13}C NMR (75.5 MHz, DMSO- d_6): δ 35.8, 51.5, 68.1, 113.0, 114.2, 121.9, 123.1, 123.7, 124.8, 126.0, 126.7, 130.6, 138.2, 144.0, 144.1, 160.5, 173.6. *Anal.* Calcd for $\text{C}_{17}\text{H}_{14}\text{O}_6$: C, 64.97; H, 4.49. Found: C, 64.57; H, 4.55.

Methyl (S)-3-(6-Hydroxy-2-oxo-2H-naphtho[2,1-b]pyranyl-3)-2-hydroxypropanoate (18). This compound was prepared from 2,7-dihydroxynaphthalene (8), reflux for 5 h; the crude product was purified by column chromatography using ether as solvent to give 18, yield 13%; mp 181–183°C (from ethyl acetate); $[\alpha]_{\text{D}}^{23} = -6.5^\circ$ ($c = 0.65$, DMF). ^1H NMR (300 MHz, DMSO- d_6): δ 2.83 (1H, dd, $J = 8.3, 13.9$ Hz, 3-Ha), 3.00 (1H, dd, $J = 4.9, 13.9$ Hz, 3-Hb), 3.65 (3H, s, OMe), 4.45 (1H, ddd, $J = 5.3, 6.0, 8.7$ Hz, 2-H), 5.67 (1H, d, $J = 6.4$ Hz, 2-OH), 7.17 (1H, dd, $J = 2.3, 9.0$ Hz, 7'-H), 7.30 (1H, d, $J = 9.0$ Hz, 10'-H), 7.65 (1H, d, $J = 2.3$ Hz, 5'-H), 7.89 (1H, d, $J = 8.7$ Hz, 8'-H), 8.00 (1H, d, $J = 9.0$ Hz, 9'-H), 8.52 (1H, s, 4'-H), 10.16 (1H, br s, 6'-OH). ^{13}C NMR (75.5 MHz, DMSO- d_6): δ 36.5, 52.4, 69.1, 105.3, 112.7, 113.7, 118.7, 123.5, 125.2, 131.5, 131.6, 133.1, 138.9, 153.7, 158.5, 161.9, 174.6. *Anal.* Calcd for $\text{C}_{17}\text{H}_{14}\text{O}_6$: C, 64.97; H, 4.49. Found: C, 65.14; H, 4.51.

Methyl (S)-3-(5,7-Dihydroxy-2-oxo-2H-benzo[b]pyranyl-3)-2-hydroxypropanoate (19). This compound was prepared from 1,3,5-trihydroxybenzene (9), reflux for 3 h; the crude product was purified by column chromatography using ethyl acetate/*n*-hexane (2 : 1) as solvent to give 19; yield 31%; mp 205–207°C (from methanol); $[\alpha]_{\text{D}}^{23} = +1.3^\circ$ ($c = 0.90$, CHCl_3). ^1H NMR (300 MHz, DMSO- d_6): δ 2.60 (1H, dd, $J = 8.3, 13.9$ Hz, 3-Ha), 2.82 (1H, dd, $J = 4.7, 13.7$ Hz, 3-Hb), 3.62 (3H, s, OMe), 4.28 (1H, ddd, $J = 4.9, 6.4, 8.3$ Hz, 2-H), 5.56 (1H, d, $J = 6.4$ Hz, OH), 6.17 (1H, d, $J = 1.9$ Hz, 6'-H), 6.26 (1H, d, $J = 2.3$ Hz, 8'-H), 7.80 (1H, s, 4'-H), 10.24 (1H, s, Het-OH), 10.56 (1H, s, Het-OH). ^{13}C NMR (75.5 MHz, DMSO- d_6): δ 35.5, 51.4, 68.4, 93.6, 98.2, 101.9, 116.6, 137.2, 155.4, 155.5, 161.2, 161.5, 173.3. *Anal.* Calcd for $\text{C}_{13}\text{H}_{12}\text{O}_7$: C, 55.72; H, 4.32. Found: C, 55.30; H, 4.30.

Methyl (S)-3-(2,5-Dioxo-5,6-dihydro-2H-pyrano[3,2-c]pyridinyl-3)-2-hydroxypropanoate (20). This compound was prepared from 4-dihydroxypyridin-2-one (**10**), reflux for 3 h; yield 64%; mp 227–229°C (from ethyl acetate); $[\alpha]_{\text{D}}^{23} = -2.1^{\circ}$ ($c = 0.78$, CHCl_3). $^1\text{H NMR}$ (300 MHz, DMSO-d_6): δ 2.66 (1H, ddd, $J = 0.8, 8.4, 13.9$ Hz, 3-Ha), 2.86 (1H, ddd, $J = 0.8, 4.5, 13.9$ Hz, 3-Hb), 3.64 (3H, s, OMe), 4.31 (1H, dt, $J = 8.3, 5.3$ Hz, 2-H), 5.62 (1H, d, $J = 6.4$ Hz, OH), 6.34 (1H, dd, $J = 7.5, 0.8$ Hz, 8'-H), 7.58 (1H, d, $J = 7.5$ Hz, 7'-H), 7.82 (1H, d, $J = 0.8$ Hz, 4'-H), 11.88 (1H, br s, 6'-H). $^{13}\text{C NMR}$ (75.5 MHz, DMSO-d_6): δ 36.1, 52.4, 68.9, 98.3, 109.1, 122.2, 139.0, 139.1, 160.9, 161.2, 163.3, 174.4. *Anal.* Calcd for $\text{C}_{12}\text{H}_{11}\text{NO}_6$: C, 54.34; H, 4.18; N, 5.28. Found: C, 54.12; H, 4.24; N, 5.37.

Methyl (S)-3-(2,5-Dioxo-7-methyl-2H,5H-pyrano[4,3-b]pyranyl-3)-2-hydroxypropanoate (21). This compound was prepared from 4-hydroxy-6-methyl-2H-pyran-2-one (**11**), reflux for 3 h; yield 65%; mp 162–164°C (from ethyl acetate); $[\alpha]_{\text{D}}^{23} = +0.9^{\circ}$ ($c = 0.57$, CH_2Cl_2). $^1\text{H NMR}$ (300 MHz, DMSO-d_6): δ 2.32 (3H, s, 7'-Me), 2.67 (1H, dd, $J = 8.5, 14.1$ Hz, 3-Ha), 2.86 (1H, dd, $J = 4.1, 13.6$ Hz, 3-Hb), 3.64 (3H, s, OMe), 4.32 (1H, dt, $J = 5.4, 7.7$ Hz, 2-H), 5.64 (1H, d, $J = 6.4$ Hz, OH), 6.64 (1H, s, 4'-H), 7.72 (1H, s, 8'-H). $^{13}\text{C NMR}$ (75.5 MHz, DMSO-d_6): δ 20.8, 35.9, 52.5, 68.7, 99.6, 101.8, 123.4, 138.8, 160.4, 160.8, 165.5, 166.4, 174.3. *Anal.* Calcd for $\text{C}_{13}\text{H}_{12}\text{O}_7$: C, 55.72; H, 4.32. Found: C, 55.28; H, 4.31.

Methyl (S)-3-(2,5-Dioxo-2H,5H-benzo[b]pyrano[4,3-b]pyranyl-3)-2-hydroxypropanoate (22). This compound was prepared from 4-hydroxy-2H-benzo[b]pyran-2-one (**12**), reflux for 2 h; yield 81%; mp 208–210°C (from ethyl acetate); $[\alpha]_{\text{D}}^{23} = -35.9^{\circ}$ ($c = 1.14$, CHCl_3). $^1\text{H NMR}$ (300 MHz, DMSO-d_6): δ 2.77 (1H, dd, $J = 8.4, 14.3$ Hz, 3-Ha), 2.95 (1H, dd, $J = 4.0, 14.2$ Hz, 3-Hb), 3.66 (3H, s, OMe), 4.38 (1H, ddd, $J = 4.7, 6.4, 8.5$ Hz, 2-H), 5.70 (1H, d, $J = 6.4$ Hz, OH), 7.48–7.55 (2H, m, 7'-H and 9'-H), 7.79 (1H, ddd, $J = 8.6, 7.2, 1.5$ Hz, 8'-H), 7.87 (1H, s, 4'-H), 8.00 (1H, br dd, $J = 7.9, 1.5$ Hz, 10'-H). $^{13}\text{C NMR}$ (75.5 MHz, DMSO-d_6): δ 35.9, 52.5, 68.7, 104.4, 113.8, 118.0, 123.7, 125.5, 126.2, 135.1, 139.1, 153.6, 159.4, 160.1, 160.6, 174.3. *Anal.* Calcd for $\text{C}_{16}\text{H}_{12}\text{O}_7$: C, 60.76; H, 3.82. Found: C, 60.77; H, 3.83.

Methyl (S)-3-(1,3-Dimethyl-2,4,7-trioxo-1,2,3,4-tetrahydro-7H-pyrano[2,3-d]pyrimidinyl-6)-2-hydroxy-propanoate (23). This compound was prepared from 1,3-dimethylbarbituric acid (**13**), reflux for 5 h; the crude product was purified by column chromatography using ethyl acetate as solvent to give **13**; yield 30%; mp 172–174°C (from ethyl acetate); $[\alpha]_{\text{D}}^{23} = +2.0^{\circ}$ ($c = 0.82$, CH_2Cl_2). $^1\text{H NMR}$ (300 MHz, DMSO-d_6): δ 2.65 (1H, ddd, $J = 0.8, 8.7, 13.9$ Hz, 3-Ha), 2.83 (1H, ddd, $J = 0.8, 4.7, 14.1$ Hz, 3-Hb), 3.23 (3H, s, Het-Me), 3.38 (3H, s, Het-Me), 3.64 (3H, s, OMe), 4.27 (1H, ddd, $J = 4.9, 8.3, 6.4$ Hz, 2-H), 5.62 (1H, d, $J = 6.4$ Hz, OH), 7.81 (1H, s, 4'-H). $^{13}\text{C NMR}$ (75.5 MHz, DMSO-d_6): δ 28.9, 29.7, 35.3, 52.5, 68.9, 93.0,

115.1, 141.2, 150.3, 158.3, 159.4, 159.7, 174.4. *Anal.* Calcd for $C_{13}H_{14}N_2O_7$: C, 50.33; H, 4.55; N, 9.03. Found: C, 50.16; H, 4.52; N, 8.87.

ACKNOWLEDGEMENT

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