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The Smallest Vicinal Tricarbonyl Compound as a Monohydrate and Tetracarbonyl Compound as a Thiane Derivative – First Effective Synthesis, Characterization and Chemistry

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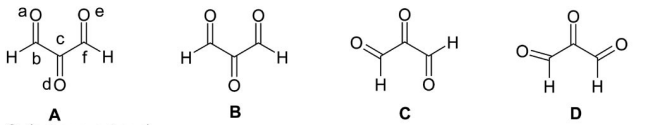
An effective synthesis of 2-oxo-1,3-propanedial monohydrate or mesoxaldehyde (**6a**) and the first synthesis of 2,3-dioxo-1,4-butanedial (**18**) as a thiane derivative are reported. These first members of the smallest vicinal tri- and tetracarbonyl compounds are stabilized by conversion to thiane derivatives **8**, **9**, **10**, **11**, **12**, **15** and **19**, which can be isolated as long-lived compounds at room temperature. The structures of these novel thianes **8**, **10**, **12** and **15** were confirmed by their X-ray crystal structures. The synthesis of a series of protected as well as free heterocyclic aldehydes (pterins and quinoxalines) by the use of the appropriate tricarbonyl compounds is also reported. Additionally, a one-step synthetic strategy to prepare a series of different biheterocycles with the smallest vicinal tetracarbonyl compound is demonstrated.

Introduction

Vicinal tri- and tetracarbonyl compounds are important synthetic building blocks and have attracted the attention of many organic chemists due to the juxtaposition of carbonyl groups within them and their high chemical reactivity.[1] These compounds are useful precursors to elaborate heterocyclic compounds[2] and numerous, novel, biologically important substances such as FK-506, rapamycin and related immunosuppressants[3] and protease inhibitors are derived from peptide carboxylic acids.[4]

In 1901, Sachs and Barschall reported the first aliphatic vicinal dimethyl triketone.[5] The historical development of the early years of vicinal triketone chemistry has recently been described,[6] and there are extensive reviews of the chemistry of vicinal polyketones.[6] However, the past 10 years have shown remarkable developments in this field, such as radical anions of acyclic vicinal oligoketones containing up to five carbonyl groups,[7] the conversion of α-bromo-β-dicarbonyl compounds to vicinal tricarbonyl compounds with dimethyldioxirane,[8] the investigation of vinyl vicinal tricarbonyl reagents (VTC)[9] and conformational studies of a vicinal triketone by ^{17}O NMR spectroscopy,[10] with important new discoveries from laboratories around the world. In 1905, Harries et al. reported[11] the preparation of mesoxaldehyde (or 2-oxo-1,3-propanedial) as a polymer from phorone or dibenzalacetone[12] and studied it in the gas phase, but found that it quickly polymerized. For this reason, the development of 2-oxo-1,3-propanedial derivatives is a continuous challenge to many chemists. Derivatives of 2-oxo-1,3-propanedial are synthesized from different sources[13] but not from 2-oxo-1,3-propanedial itself. The four conformations **A**–**D** of 2-oxo-1,3-propanedial have also been theoretically examined at the RHF/6-31G* level of theory.[9]



Except for the derivatives of 2-oxo-1,3-propanedial (or mesoxaldehyde), no systematic survey of the chemistry of this smallest VTC has appeared. The present work is an attempt to fill this gap in the synthesis and chemistry of these compounds, which at present, is scattered over more than 100 years in chemistry.

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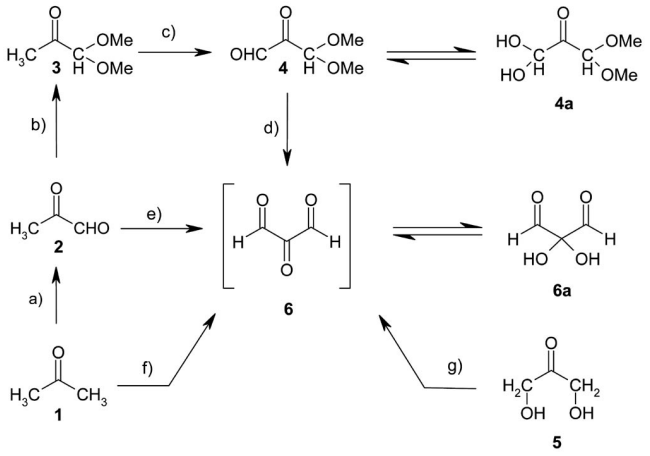
Herein, we report the synthesis, characterization and chemistry of 2-oxo-1,3-propanedial (**6**) as its hydrate, 3,3-dimethoxy-2-oxopropanal (**4**) and the crystal structure of dithiane derivatives of 2-oxo-1,3-propanedial **8**, **10** and **12**. We also report the first synthesis of the first member of the smallest teracarbonyl compound, which was not freely isolated but characterized as a new long-lived thiane derivative **19**. To the best of our knowledge, this smallest tetracarbonyl compound has not been reported in the literature in the free state or as a protected derivative. The one-step synthesis of novel biheterocycles has been achieved from this first member of the tetracarbonyl compounds. Since the classical biheterocycles are always synthesized by long linear sequences,[14] a one-step synthesis of biheterocycles would be advantageous in synthetic organic chemistry. In our efforts, we have succeeded in synthesizing challenging, functionalized, biheterocycles (e.g. pterin, quinoxaline and pyridopyrazines) in one step.



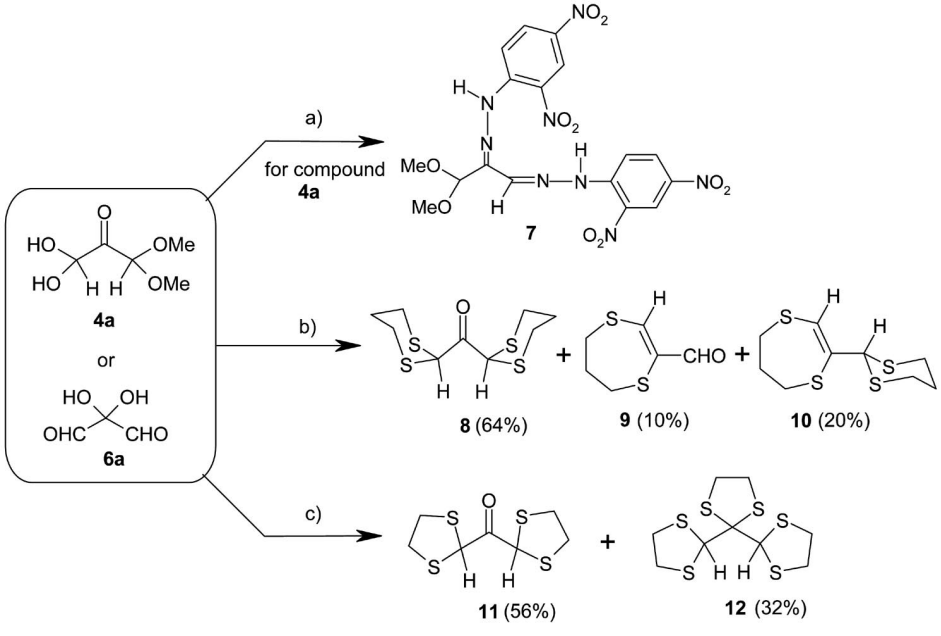
Scheme 1. Synthesis of the smallest vicinal tricarbonyl compound as monohydrate **6a**. Reagents and conditions: (a) SeO_2 80 °C, 12 h, 74%; (b) dry MeOH, concentrated H_2SO_4, benzene, 16 h, 86%; (c) SeO_2, 80 °C, 9 h, 85%; (d) HCOOH, $CHCl_3$, room temp., 7 h, 54%; (e) 1.5 equiv. SeO_2, dry dioxane, 100 °C, 8 h, 45%; (f) 2.5 equiv. SeO_2, dry dioxane, 100 °C, 16 h, 58%; (g) $Cu(OAc)_2$, H_2O, 100 °C, 12 h, 42%.

Results and Discussion

Our successful approach to prepare 2-oxo-1,3-propanedial (**6**) by this new, simple and efficient method in good yield is delineated in Scheme 1 and led to its effective isolation. We carried out the conversion of acetone to 1,2-dimethoxypropanone (**3**) with the standard procedure.[15] The reaction between 1,2-dimethoxypropanone (**3**) and selenium dioxide in dry dioxane at reflux produced the important compound **4** in 85% yield as a golden oil. Compound **4**, upon careful hydrolysis, provided the semisolid product **6a** in 54% yield (Scheme 1). We also prepared **6a** from 2-oxopropanal (**2**) or acetone directly by treating it with 1 or 2.5 equiv. of selenium dioxide, respectively, in dry dioxane at reflux in 45 or 58% yield, respectively.

We succeeded in converting 1,3-dihydroxyacetone (**5**) to 2-oxo-1,3-propanedial (**6**, 42% yield) by refluxing the starting material with copper acetate in dry dioxane for 12 h. However, we found the formation of **6** from **2** by this direct route to be more efficient. Polyketones are generally present as hydrates, which are stable in the solid state. Preferential hydration at a central carbonyl group is usually observed.

In our case, 3,3-dimethoxy-2-oxopropanal (**4**) and 2-oxo-1,3-propanedial (**6**) also existed as hydrated forms **4a** and **6a**. The hydration occurred at a terminal aldehyde group in



Scheme 2. Synthesis of novel, long-lived, thiane derivatives of **4a** and **6a**. Reagents and conditions: (a) (2,4-dinitrophenyl)hydrazine, concentrated H_2SO_4, H_2O bath, 25 min, 62%; (b) 1,3-propanedithiol, $BF_3{\cdot}Et_2O$, 0 °C, 3 h; (c) 1,2-ethanedithiol, $BF_3{\cdot}Et_2O$, 0 °C, 4 h.

4 and at the central carbonyl group in **6**, which was confirmed by ^{1}H NMR spectroscopy and mass spectrometry. Compound **4a** produced hydrazone derivative **7** with (2,4-dinitrophenyl)hydrazine (Scheme 2).

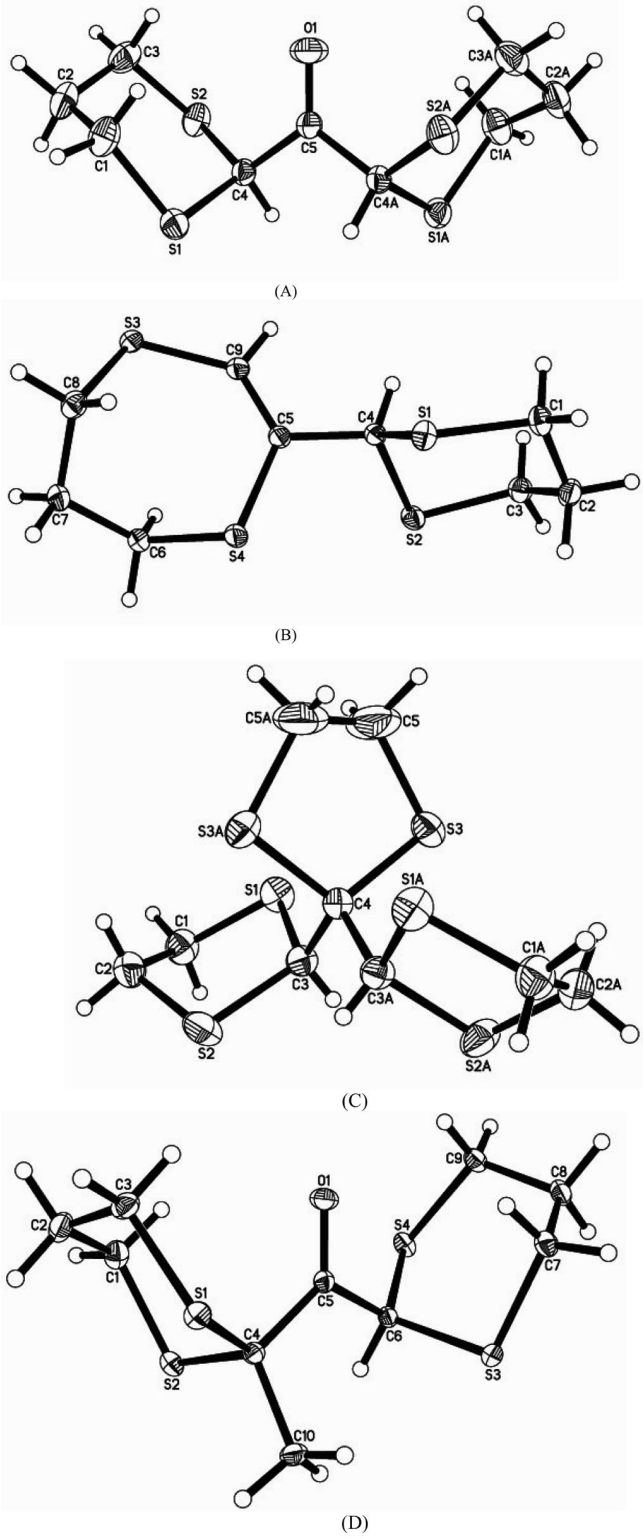


Figure 1. ORTEP representation of dithianes **8** (A), **10** (B), **12** (C) and **15** (D).

The synthesis of the novel cyclic thianes **8**, **9**, **10**, **11** and **12** is of fundamental significance. Upon the condensation of 1,3-propanedithiol with 2,2-dihydroxy-1,3-propanedial (**6a**) at 0 °C, we obtained **8** as the major product, along with **9** and **10**. We also isolated **8**, **9** and **10** when 1,1-dihydroxy-3,3-dimethoxy-2-propanone (**4a**) was condensed with 1,3-propanedithiol and in better yields than in the **6a** case. We also accomplished an efficient preparation of thiane derivatives **11** and **12** from 2,2-dihydroxy-1,3-propanedial (**6a**) upon treatment with excess 1,2-ethanedithiol. Our development of new, hydrazone-free modes of protection and liberation of the free tricarbonyl compounds is an obvious advantage.

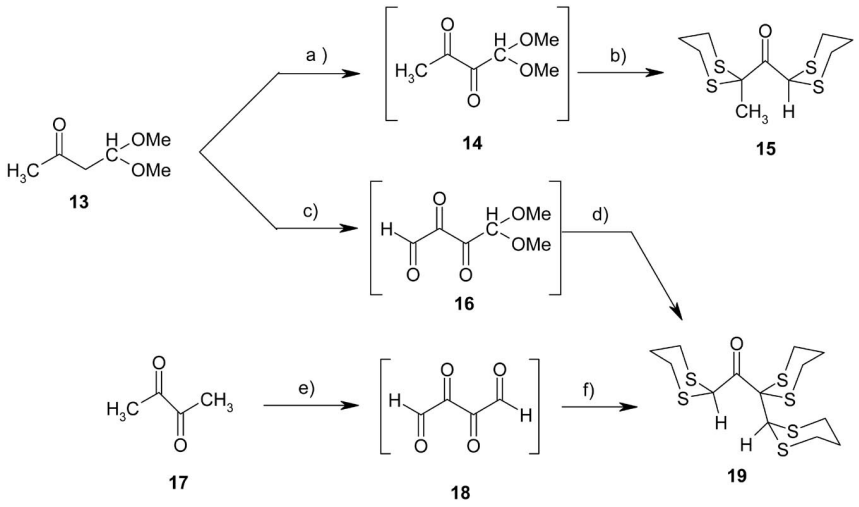
We confirmed the structures of **4a** and **6a** by spectroscopic methods (IR, ^{1}H NMR and MS); the appearance of a single carbonyl absorption band in the IR spectrum, a singlet for the α-proton of the carbonyl group in the ^{1}H NMR spectrum as well as the $[M]^+$ peak in the mass spectrum agreed completely with the proposed structure. We obtained final structural confirmation of all the thiane derivatives **8**, **10** and **12** by X-ray crystal structure investigations (Figure 1), the details of which can be found in the Supporting Information (Tables I and II).

We efficiently synthesized the smallest vicinal tetracarbonyl compounds 2,3-dioxo-1,4-butanedial (**18**) and 4,4-dimethoxy-2,3-dioxobutanal (**16**) from **17** and **13**, respectively, by SeO_2 oxidation in dry dioxane at 70–75 °C (Scheme 3). We noted that the reaction temperature should not exceed 75 °C. Above 75 °C, 2,3-dioxo-1,4-butanedial (**18**) and 4,4-dimethoxy-2,3-dioxobutanal (**16**) were highly unstable and quickly polymerized; therefore, we took these to the next step without further purification. Upon reaction with 1,3-propanedithiol, the crude reaction products afforded **19** in a maximum yield of 65%. We achieved the synthesis of the new thiane derivative **15** by starting from 4,4-dimethoxybutan-2-one (**13**, Scheme 3) via intermediate **14**. We performed an X-ray crystal structure determination of **15** at low temperature (Figure 1, D).

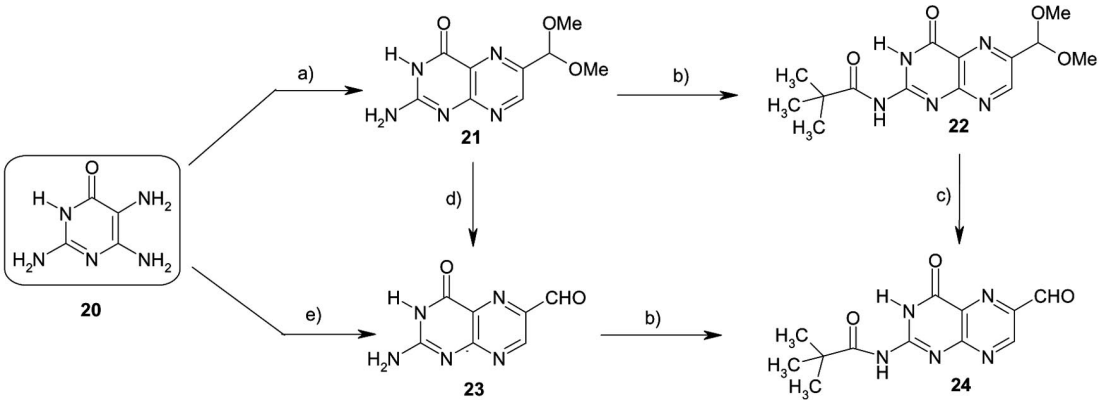
Chemistry of Tri- and Tetracarbonyl Compounds

The Gabriel–Isay pteridine synthesis between 2,5,6-triaminopyrimidin-4(3*H*)-one and an unsymmetrical α,β-dicarbonyl compound leads to the preferential formation of the unwanted 7-substituted isomer rather than the 6-substituted isomer.[16] Previously in our laboratory, we reported the one-pot synthesis of the 6-substituted isomer.[17]

In our continuing interest in the synthesis of 6-formylpterin,[18,19] a useful precursor to the nutrient cofactor folic acid, the anticancer drug methotrexate[20] and related pteridines like biopterin, neopterin and precursor Z of molybdenum cofactor (Moco),[21] we have used the mesoxaldehyde and its monoacetal in a useful, straightforward and economic method for the first synthesis of the dimethyl acetal of the 6-formylpterin **21** and its conversion to the 6-formylpterin **23** (Scheme 4).



Scheme 3. Synthesis of [2,2′-bi(1,3-dithianyl)-2-yl](1,3-dithian-2-yl)methanone (**19**), a novel thiane derivative of the smallest vicinal tetracarbonyl compound [i.e. 2,3-dioxo-1,4-butanedial (**18**)]. Reagents and conditions: (a) 1.5 equiv. SeO_2, dry dioxane, 100 °C, 12 h, 74%; (b) 1,3-propanedithiol, $BF_3{\cdot}Et_2O$, 0 °C, 2.5 h, 56%; (c) 2.5 equiv. SeO_2, dry dioxane, 75 °C, 8 h, 65%; (d) 1,3-propanedithiol, $BF_3{\cdot}Et_2O$, 0 °C, 3 h, 42%; (e) 2.5 equiv. SeO_2, dry dioxane, 70–75 °C, 12 h, 52%; (f) 1,3-propanedithiol, $BF_3{\cdot}Et_2O$, 0 °C, 1 h, 36%.

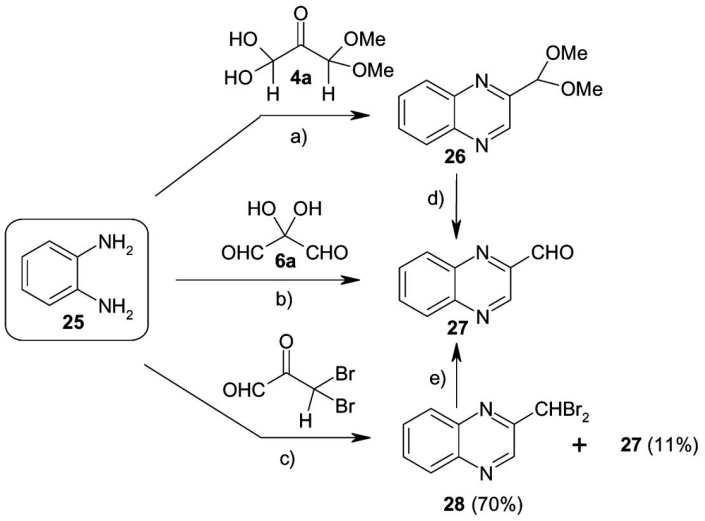


Scheme 4. Synthesis of 6-formylpterin dimethyl acetal **21** and 6-formylpterin **23**. Reagents and conditions: (a) 1,1-dihydroxy-3,3-dimethoxy-2-propanone, $NaHSO_3$, H_2O, 12 h, 54%; (b) pivalic anhydride, DMAP, 90 °C, 6 h, 71%; (c) CF_3COOH, $CHCl_3$ and H_2O, 3 h, 92%; (d) 1 N HCl in dioxane, 98%; (e) 2,2-dihydroxy-1,3-propanedial, H_2O, 16 h, 55%.

The general and multistep synthesis of 7-formylpterin dimethyl acetal was first elegantly performed by Taylor et al.[22] We report herein our success in achieving a facile, regiospecific synthesis of 6-formylpterin dimethyl acetal **21** (Scheme 4) by the condensation of 2,5,6-triaminopyrimidin-4(3*H*)-one dihydrochloride (**20**) and 1,1-dihydroxy-3,3-dimethoxy-2-propanone (**4a**) with sodium hydrogen sulfate at 0–5 °C in 54% yield as a yellow crystalline solid, which upon treatment with 1 N HCl gave **23** in almost quantitative yield. We also prepared **23** by the direct addition of triaminopyrimidine (**20**) to the free tricarbonyl compound **6a** in 55% yield.

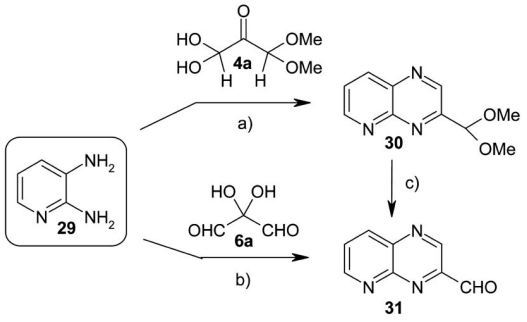
Since pterins are extremely poorly soluble[17] in both organic and aqueous media, we performed the ^1H NMR spectroscopic studies of the 6-substituted pterins **22** and **24** on their 2-pivaloylamide derivatives **21** and **23**, respectively. We also isolated 6-formyl-2-(pivaloylamino)pterin (**24**) from **22** upon hydrolysis with TFA.

The synthesis of quinoxalinecarbaldehydes has been reported in various ways from *o*-phenylenediamine over multiple steps.[18,23] Now we have applied the tricarbonyl compound **6a** to the one-step synthesis of a quinoxalinecarbaldehyde, as shown in Scheme 5. Refluxing of *o*-phenylenediamine (**25**) with **4a** in dry ethanol gave the crystalline solid **26**. We hydrolyzed this intermediate with formic acid in H_2O and $CHCl_3$ and isolated only 2-quinoxalinecarbaldehyde (**27**) in an overall 90% yield. Using 2,2-dihydroxy-1,3-propanedial (**6a**) instead of **4a**, we obtained 2-quinoxalinecarbaldehyde. In an interesting case, the condensation of *o*-phenylenediamine (**25**) with 3,3-dibromo-2-oxopropanal in ethanol gave the 2-quinoxalinecarbaldehyde as the major isolable product along with some 2-(dibromomethyl)-quinoxaline (**28**). Our new and efficient approach to the synthesis of 2-quinoxalinecarbaldehyde by various ways is summarized in Scheme 5. We also similarly synthesized 3-(dimethoxymethyl)pyrido[2,3-*b*]pyrazine (**30**) and pyr-



Scheme 5. Synthesis of 2-(dimethoxymethyl)quinoxaline (**26**) and 2-quinoxalinecarbaldehyde (**27**). Reagents and conditions: (a) 3,3-dimethoxy-2-oxopropanal, dry EtOH, reflux, 4 h, 85%; (b) 2,2-dihydroxypropanedial, dry EtOH, reflux, 4 h, 92%; (c) 3,3-dibromo-2-oxopropanal, dry EtOH, reflux, 6 h, 70%; (d) HCOOH, H_2O and $CHCl_3$, room temp., 5 h, 94%; (e) NaOH, reflux, 3 h, 84%.

ido[2,3-*b*]pyrazine-3-carbaldehyde (**31**) from pyridine-2,3-diamine (**29**) using 1,1-dihydroxy-3,3-dimethoxy-2-propanone (**4a**) and 2,2-dihydroxy-1,3-propanedial (**6a**), respectively (Scheme 6).



Scheme 6. Synthesis of 3-(dimethoxymethyl)pyrido[2,3-*b*]pyrazine (**30**) and pyrido[2,3-*b*]pyrazine-3-carbaldehyde (**31**). Reagents and conditions: (a) 1,1-dihydroxy-3,3-dimethoxy-2-propanone, dry EtOH, reflux, 8 h, 85%; (b) 2,2-dihydroxy-1,3-propanedial, dry EtOH, reflux, 6 h, 57%; (c) HCOOH, in H_2O and $CHCl_3$, room temp., 6 h, 82%.

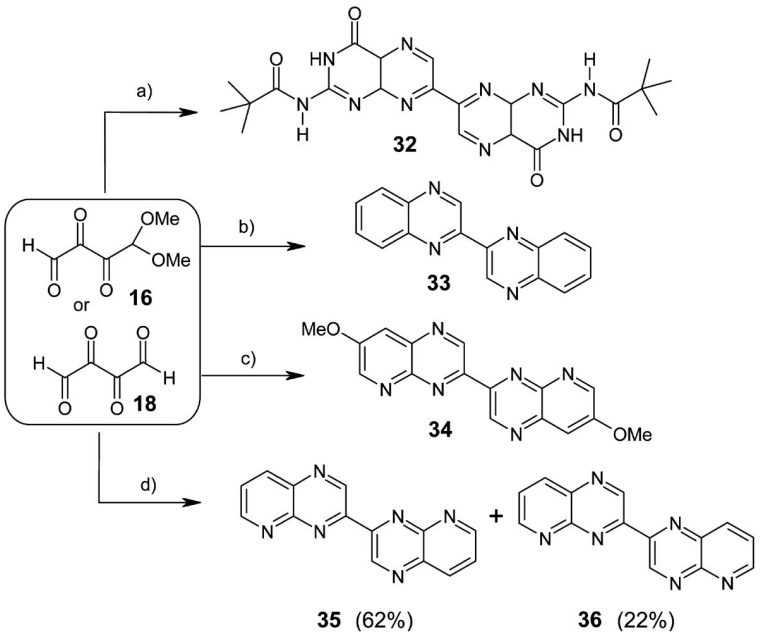
We prepared a series of biheterocycles **32**–**36** by reaction of the smallest vicinal tetracarbonyl compound, 2,3-dioxo-1,4-butanedial (**18**) or 4,4-dimethoxy-2,3-dioxobutanal (**16**), with the appropriate 1,2-diamino heterocyclic compound (Scheme 7). When 2,3-diaminopyridine was condensed with **16** or **18**, we isolated 3,3′-bi[pyrido[2,3-*b*]pyrazinyl] (**35**) as the major product, along with the minor product **36**. We confirmed all the biheterocycles **32**–**36** by NMR spectroscopy and mass spectrometry. We obtained final structural confirmation of **33**[24] and **35** by X-ray crystallographic investigations (Figure 2).

Conclusions

Based on the progress reported herein, we expect the future of VTC chemistry to show many more new and useful developments that exploit the unique structure and reactivity of this family. We thus achieved the following: (1) the first effective synthesis of the smallest vicinal tricarbonyl compound, 2-oxo-1,3-propanedial, as its hydrate **6a**, tetracarbonyl compound 2,3-dioxo-1,4-butanedial (**18**) as its thiane derivative, and the extensive synthesis and single-crystal X-ray confirmation of other novel thiane derivatives, (2) new strategies for the synthesis of 6-formylpterin dimethyl acetal (**22**), pterincarbaldehyde **24** and 2-quinoxalinecarbaldehyde (**27**), and (3) the one-step synthetic access of biheterocycles **32**–**36** from simple 1,2-diamino aromatic or heterocyclic compounds and the smallest tetracarbonyl compound.

Experimental Section

2-Oxopropanal (2): SeO_2 (40 g) and acetone (200 mL) were heated at reflux for 10–12 h, carefully during the initial stage, when the reaction was exothermic. The yellow liquid product was decanted, the black residue was washed with acetone, and the whole liquid was fractionally distilled. The pale yellow distillate (b.p. 56.5 °C, 160 mL was collected up to 80 °C) was an azeotropic mixture of acetone containing approximately 1% of **2**. The residual liquid was fractionally distilled under reduced pressure. The higher boiling fraction condensed as a bright yellow, mobile liquid that polymerized. The lower boiling fraction, which contained a greater proportion of H_2O, simply became viscous. The yield of **2** (containing a little H_2O, b.p. 68 °C–80 °C) was 19 g (74%). R_f = 0.4 (CH_2Cl_2/petroleum ether, 1:1). ^1H NMR ($CDCl_3$, 500 MHz): δ = 9.07 (s, 1 H), 2.06 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 207.57, 161.00, 30.60 ppm.



Scheme 7. Synthesis of biheterocycles **32**–**36** by using the smallest tetracarbonyl compounds **16** and **18**. Reagents and conditions: (a) 2,5,6-triaminopyrimidin-4(3*H*)-one dihydrochloride, H_2O, 0–5 °C; then pivalic anhydride, DMAP, 90 °C, 8 h, 46%; (b) *o*-phenylenediamine, dry EtOH, reflux, 7 h, 64%; (c) 2,3-diamino-5-bromopyridine, dry MeOH, reflux, 7 h, 57%; (d) 2,3-diaminopyridine, dry MeOH, reflux, 7 h.

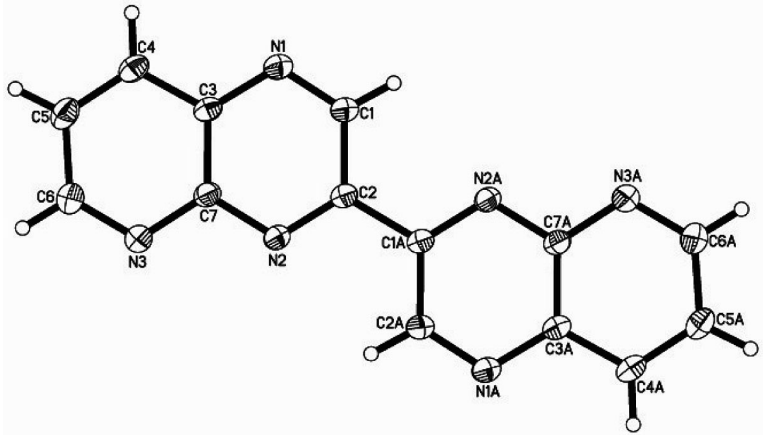


Figure 2. ORTEP representation of the biheterocycle 3,3′-bi[pyrido[2,3-*b*]pyrazinyl] (**35**).

1,1-Dimethoxy-2-propanone (3): A solution of **2** (10.0 g) in dry MeOH (100 mL) with a catalytic amount of *p*-toluenesulfonic acid (1 g) was stirred at room temperature for 12 h. When most of the starting material was converted into products (monitored by TLC), the reaction mixture was distilled to collect **3** at 125–130 °C. The yield was 14 g (86%). R_f = 0.72 (CH_2Cl_2/petroleum ether, 1:1). ^1H NMR ($CDCl_3$, 500 MHz): δ = 4.31 (s, 1 H), 3.28 (s, 6 H), 2.07 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 203.39, 103.94, 54.39, 24.57 ppm.

1,1-Dihydroxy-3,3-dimethoxypropan-2-one (4a): A mixture of SeO_2 (500 mg, 4.5 mmol) and **3** (500 mg, 4.2 mmol) was partially dissolved in dry dioxane (3 mL) in a round-bottomed flask. The flask was then heated at 70–80 °C for 9 h, and the remaining yellow liquid was dissolved in chloroform and passed through a pad (3–4 cm) of Celite. The filtrate was concentrated to dryness with a rotary evaporator and purified by column chromatography (silica gel, 100–200 mesh) by using chloroform/petroleum ether (1:3); the product was a viscous, golden liquid (**4a**, 478 mg, 85%). R_f = 0.6 (CH_2Cl_2/hexane, 1:1). FT-IR (KBr): $\tilde{\nu}_{max}$ = 3387, 1735, 1638, 1061, 895 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 4.88 (s, 1 H), 4.36 (br. s, 2 OH), 3.79 (s, 1 H), 3.73 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.1, 93.6, 49.26, 30.0 ppm. MS (EI): *m*/*z* (%) = 132 (2) $[M - H_2O + H]^+$, 101 (8) $[M - OMe]^+$, 75 (100), 47 (18), 29 (25).

2,2-Dihydroxy-1,3-propanedial (6a): A mixture of **4a** (1 g, 7.1 mmol), formic acid (4 mL), chloroform (1 mL) and H_2O (10 mL) was stirred at room temperature for 7 h The mixture was neutralized with saturated $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), filtered and concentrated in vacuo to give a white semi-solid compound, which was purified by silica gel column chromatography to give a white semisolid **6a** (0.319 g, 54%). A mixture of SeO_2 (275 mg, 2.5 mmol) and **2** (40%, 142 mg, 2 mmol) was partially dissolved in a round-bottomed flask and refluxed in

a H_2O bath at 70–80 °C for 8 h. The remaining yellow liquid was dissolved in chloroform and filtered through a pad (3–4 cm) of Celite. The filtrate was concentrated to dryness with a rotary evaporator and purified by thin layer chromatography using chloroform/petroleum ether (3:1) to afford white semisolid **6a** (94 mg, 45%). To a stirred solution of **1** (2 mL) in dioxane (4 mL), SeO_2 (7.10 g, 0.06 mol) was added, and the mixture was heated at 100 °C for 16 h. The remaining yellow solution was dissolved in chloroform/MeOH, filtered through a pad (3–4 cm) of Celite and washed well with chloroform. The filtrate was concentrated to dryness with a rotary evaporator and purified by thin layer chromatography using silica gel (100–200 mesh) to afford **6a** (1.50 g, 58%) in good yield. Copper acetate (2 g, 0.01 mol) was dissolved in H_2O (10 mL), and **5** (500 mg, 5.5 mmol) was added. The resulting mixture was heated at reflux for 12 h, cooled to 25 °C and then extracted with chloroform. The organic layer was dried (anhydrous Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was purified on silica gel by using chloroform/petroleum ether (3:1) to give **6a** (240 mg, 42%) as a white semisolid. R_f = 0.4 (CH_2Cl_2/hexane, 2:1). FT-IR (KBr): $\tilde{\nu}_{max}$ = 3389, 2850, 1729 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.03 (s, 2 H), 4.62 (br. s, 2 OH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 222.8, 214.9 ppm. MS (EI): *m*/*z* (%) = 104 (14) $[M]^+$, 86 (2) $[M - H_2O]^+$, 85 (35) $[M - 1]^+$, 57 (95) $[M - CHO]^+$.

3,3-Dimethoxy-2-oxopropanal 1,2-Bis[(2,4-dinitrophenyl)hydrazone] (7): A solution of 3,3-dimethoxy-2-oxopropanal (500 mg, 3.5 mmol) in H_2O (10 mL) was treated with (2,4-dinitrophenyl)hydrazine (1.42 g, 7.17 mmol) in MeOH (10 mL) and a few drops of acetic acid. The mixture was warmed in a water bath for 25 min and then cooled. The product that separated was filtered off, washed and dried. It was crystallized from MeOH/chloroform to give yellow needles (1.09 g, 62%). R_f = 0.6 (EtOAc/hexane, 1:5); m.p. 210–215 °C (dec.). FT-IR (KBr): $\tilde{\nu}_{max}$ = 3274, 2359, 1333, 1139, 832 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 13.25 (br. s, 1 H), 11.49 (br. s, 1 H), 9.17 (d, *J* = 2.41 Hz, 2 H), 8.51–8.42 (m, 2 H), 8.35–8.26 (m, 2 H), 7.95 (s, 1 H), 4.91 (s, 1 H), 3.53 (s, 3 H), 3.49 (s, 3 H) ppm. MS (ESI): *m*/*z* (%) = 495 (20) $[M + 2]^+$, 433 (35), 269 (100). $C_{17}H_{16}N_8O_{10}$ (492.36): calcd. C 41.47, H 3.28, N 22.76; found C 41.48, H 3.24, N 22.82.

Bis(1,3-dithian-2-yl)methanone (8), 6,7-Dihydro-5*H*-1,4-dithiepine-2-carbaldehyde (9) and 2-(1,3-Dithian-2-yl)-6,7-dihydo-5*H*-1,4-dithiepine (10): To a stirred solution of **4a** (500 mg, 4.1 mmol) and boron trifluoride–diethyl ether (0.5 mL) in CH_2Cl_2 (50 mL), cooled to 0 °C, was added 1,3-propanedithiol (450 mg, 4.1 mmol) dropwise with stirring over 15 min. The mixture was stirred at room temperature for 3 h. With respect to the starting material, three less polar spots (products) were generated as indicated by TLC. Aqueous $NaHCO_3$ was added slowly and carefully to neutralize the mixture at room temperature, which was then extracted with CH_2Cl_2. The organic layer was dried (anhydrous Na_2SO_4), and the solvent was then removed under reduced pressure. The crude product was purified on silica gel by preparative TLC using petroleum ether in chloroform (20%). Compound **8** was isolated as a white crystalline solid (610 mg, 64%), compound **9** (57 mg, 10%) was obtained from the less polar spot with respect to **8**, and compound **10** (179 mg, 20%) was isolated from the more polar spot with respect to **8**.

8: R_f = 0.25 (CH_2Cl_2/petroleum ether, 1:5); m.p. 139–142 °C. FT-IR (KBr): $\tilde{\nu}_{max}$ = 2923, 2360, 1684, 1540, 1020 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 4.63 (s, 2 H), 3.36 (t, *J* = 12.99 Hz, 2 H), 2.61 (t, *J* = 3.99 Hz, 3 H), 2.56 (t, *J* = 4.00 Hz, 3 H), 2.08 (t, *J* = 2.91 Hz, 1 H), 2.04 (t, *J* = 2.92 Hz, 1 H), 2.00 (t, *J* = 2.47 Hz, 1 H), 1.87 (t, *J* = 2.21 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 194.1, 43.8, 30.1, 26.2, 25.4 ppm. MS (FAB): *m*/*z* (%) = 266 (100) $[M]^+$. $C_9H_{14}OS_4$ (266.45): calcd. C 40.57, H 5.30; found C 40.52, H 5.39. Crystal data: Empirical formula $C_9H_{14}OS_4$, formula mass 266.48, crystal system orthorhombic, space group *Pbcn* (no. 60), cell parameters: *a* = 6.8344(1), *b* = 18.0589(2), *c* = 9.4376(1) Å, *Z* = 4, D_c = 1.520 g/cm^3, μ(Mo-K_α) = 0.780 mm^{-1}, *F* (000) = 560, crystal size 0.26 × 0.35 × 0.87 mm, *T* = 293 K, λ(Mo-K_α) = 0.71073 Å, $\theta_{min/max}$ = 3.8/35.0°, total/unique data/*R*(int) = 19423/2550/0.020, observed data = 2219 [$I > 2.0\sigma(I)$], N_{ref} = 2550, N_{par} = 65, *R* = 0.0264, *wR*2 = 0.0730.

9: R_f = 0.3 (CH_2Cl_2/petroleum ether, 1:5); m.p. 110–113 °C. FT-IR (KBr): $\tilde{\nu}_{max}$ = 2910, 2359, 1716, 1540, 1418 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 9.09 (s, 1 H), 4.47 (s, 1 H), 3.09 (t, *J* = 12.34 Hz, 1 H), 2.94 (dd, *J* = 5.30, 3.52 Hz, 1 H), 2.68 (t, *J* = 3.76 Hz, 1 H), 2.64 (t, *J* = 3.72 Hz, 1 H), 2.10 (m, 1 H), 1.88 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 186.2, 53.4, 32.1, 27.6, 26.1, 24.5 ppm. MS (FAB): *m*/*z* (%) = 162 (100) $[M + 2]^+$. $C_6H_8OS_2$ (160.26): calcd. C 44.97, H 5.03; found C 44.99, H 5.12.

10: R_f = 0.6 (CH_2Cl_2/petroleum ether, 1:5); m.p. 102–104 °C. FT-IR (KBr): $\tilde{\nu}_{max}$ = 2925, 1408, 1275, 1099 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 6.28 (s, 1 H), 4.48 (s, 1 H), 3.37 (m, 4 H), 2.83 (dd, *J* = 3.54, 3.96 Hz, 4 H), 2.07 (m, 2 H), 1.82 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 122.5, 33.1, 31.4, 30.8, 29.8, 25.2 ppm. MS (FAB): *m*/*z* (%) = 248 (50) $[M - 2]^+$. $C_9H_{14}S_4$ (250.45): calcd. C 43.16, H 5.63; found C 43.20, H 5.70. Crystal data: Empirical formula $C_9H_{14}S_4$, formula mass 250.48, crystal system monoclinic, space group $P2_1/n$ (no.14), cell parameters: *a* = 11.0556(3), *b* = 9.2418(2), *c* = 12.1246(3) Å, β = 114.900(1) Å, *Z* = 4, D_c = 1.481 g/cm^3, μ(Mo-K_α) = 0.797 mm^{-1}, *F*(000) = 528, crystal size 0.12 × 0.19 × 0.64 mm, *T* = 100 K, λ(Mo-K_α) = 0.71073 Å, $\theta_{min/max}$ = 32.1/37.5°, total/unique data/*R*(int) = 46826/5846/0.036, observed data = 4998 [$I > 2.0\sigma(I)$], N_{ref} = 5547, N_{par} = 174, *R* = 0.0284, *wR*2 = 0.0735.

Bis(1,3-dithiolan-2-yl)methanone (11) and 2,2′;2′,2′′-Ter(1,3-dithiolan-2-yl) (12): To a stirred mixture of **4a** (500 mg, 3.33 mmol) or **6a** (400 mg, 3.8 mmol) and 1,2-ethanedithiol (400 mg, 3.8 mmol) in CH_2Cl_2 (15 mL) was added boron trifluoride–diethyl ether (0.5 mL) at 0–5 °C. The reaction mixture was stirred at room temperature and monitored by TLC until the starting material had disappeared. After completion of the reaction, the mixture was neutralized by the addition of aqueous $NaHCO_3$ (5%), washed with H_2O and extracted with CH_2Cl_2. The organic layer was concentrated under reduced pressure. The crude reaction mixture was purified by silica gel column chromatography eluting with petroleum ether/CH_2Cl_2 (1:3), which first afforded **11** as a white crystalline solid (440 mg, 56%), followed by **12** as a yellow solid (330 mg, 32%).

11: R_f = 0.4 (CH_2Cl_2/petroleum ether, 1:1); m.p. 142–144 °C. FT-IR (KBr, $\tilde{\nu}_{max}$ = 2926, 2853, 1703, 1215, 785 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.178 (s, 2 H), 3.35–3.30 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 196.3, 54.4, 39.1, 29.6 ppm. MS (FAB): *m*/*z* (%) = 237 (20) $[M - 1]^+$, 130 (100). $C_7H_{10}OS_4$ (238.40): calcd. C 35.26, H 4.23; found C 35.39, H 4.35.

12: R_f = 0.6 (CH_2Cl_2/petroleum ether, 1:1); m.p. 133–135 °C. FT-IR (KBr): $\tilde{\nu}_{max}$ = 2918, 2849, 1660, 1090, 772 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.16 (s, 2 H), 3.48 (t, *J* = 6.36 Hz, 2 H), 3.41 (s, 1 H), 3.37–3.34 (m, 4 H), 3.32–3.29 (q, 4 H), 3.22–3.17 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 63.6, 38.4, 30.0 ppm. $C_9H_{14}S_6$ (314.57): calcd. C 34.36, H 4.49; found C 34.42, H 4.51. Crystal data: Empirical formula $C_9H_{14}S_6$, formula mass 314.56, crystal system orthorhombic, space group *Aba*2 (no. 41), cell parameters: *a* = 10.1586(2), *b* = 15.5169(4), *c* = 8.0488(2) Å, *V* = 1268.73(5) $Å^3$,

Z = 4, D_c = 1.626 g/cm^3, μ(Mo-K_α) = 1.042 mm^{-1}, F (000) = 656, Crystal Size = 0.30 × 0.32 × 0.47 mm, Temperature = 266 K, Radiation (Mo-K_α) = 0.71073 Å, $\theta_{min/max}$ = 2.6/34.6°, total/unique data/R(int) = 10732/2697/0.028, observed data = 2267 [$I > 2.0\sigma(I)$], N_{ref} = 2697, N_{par} = 89, R = 0.0381, $wR2$ = 0.1072.

(1,3-Dithian-2-yl)(2-methyl-1,3-dithian-2-yl)methanone (15): The experimental procedure for the preparation of **15** was the same as that described for the preparation of **8** from **4a**. Starting from **14** (0.450 g, 0.003 mol), **15** (0.480 g, 56%) was generated as a yellow crystalline solid after chromatographic separation; m.p. 129–131 °C. R_f = 0.7 (CH_2Cl_2/petroleum ether, 1:1). FT-IR (KBr): $\tilde{\nu}_{max}$ = 2924, 2365, 1685, 1540, 1262 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.80 (s, 1 H), 3.54 (t, J = 9.88 Hz, 2 H), 3.14 (t, J = 10.26 Hz, 2 H), 2.67 (t, J = 2.79 Hz, 1 H), 2.62 (t, J = 2.73 Hz, 1 H), 2.57 (t, J = 3.22 Hz, 1 H), 2.53 (t, J = 2.94 Hz, 1 H), 2.20 (m, 1 H), 2.09 (m, 1 H), 2.03 (m, 1 H), 1.79 (m, 1 H), 1.83 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 197.4, 56.7, 36.6, 28.7, 25.8, 25.64, 25.2, 24.1 ppm. MS (FAB): m/z (%) = 281 (13) [M + H]$^+$, 191 (68), 147 (100). $C_{10}H_{16}OS_4$ (280.48): calcd. C 42.82, H 5.75; found C 42.89, H 5.77. Crystal data: Empirical formula $C_{10}H_{16}OS_4$, formula mass 280.51, crystal system triclinic, space group $P\bar{1}$ (no. 2), cell parameters: a = 6.6966(1), b = 8.6519(1), c = 11.9482(1) Å, α = 95.958(1), β = 106.051(1), γ = 104.183(1)°, Z = 2, D_c = 1.469 g/cm^3, μ(Mo-K_α) = 0.721 mm^{-1}, F(000) = 296, crystal size 0.20 × 0.39 × 0.45 mm, T = 100 K, λ(Mo-K_α) = 0.71073 Å, $\theta_{min/max}$ = 1.8/35.0°, total/unique data/R(int) = 15424/5547/0.016, observed data = 5195 [$I > 2.0\sigma(I)$], N_{ref} = 5547, N_{par} = 137, R = 0.0211, $wR2$ = 0.0587.

4,4-Dimethoxy-2,3-dioxobutanal (16): A mixture of SeO_2 (4 g, 0.036 mol) and **3** (2 g, 0.015 mol) was partially dissolved in dioxane (15 mL) in a round-bottomed flask. The flask was then heated at 70–80 °C for 8 h, and the remaining yellow liquid was dissolved in chloroform/MeOH (1:1) and passed through a pad (3–4 cm) of Celite. The filtrate was concentrated to dryness with a rotary evaporator under reduced pressure. The gummy **16** (1.43 g, 65%) was then directly used for thioacetalization or other reactions.

2,3-Dioxo-1,4-butanedial (18): A mixture of 2,3-dioxobutanone (5 g, 0.058 mol), SeO_2 (15 g, 0.136 mol) and dioxane (10 mL) was carefully heated under reflux for 8 h, and the reaction mixture was cooled to room temperature. The yellow liquid left was dissolved in chloroform/MeOH (1:1) and passed through a pad (3–4 cm) of Celite. The filtrate was then concentrated under reduced pressure to afford the title compound **18** (3.44 g, 52%), which was not further purified, but directly used for thioacetalization or other reactions.

[2,2′-Bi(1,3-dithianyl-2-yl)](1,3-dithian-2-yl)methanone (19): The experimental procedure for the preparation is the same as that described for the preparation of **8** from **4a**. Starting from **18** (400 mg, 4.38 mmol), **19** (600 mg, 36%) was generated as a yellow crystalline solid after column chromatographic separation. R_f = 0.6 (CH_2Cl_2/petroleum ether, 1:1); m.p. 148–151 °C. FT-IR (KBr): $\tilde{\nu}_{max}$ = 2917, 2848, 1714, 1641, 1095, 1040, 772 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.79 (s, 1 H), 3.53 (t, J = 13.20 Hz, 4 H), 3.13 (t, J = 13.20 Hz, 4 H), 2.64 (tt, J = 3.56, 3.58 Hz, 4 H), 2.54 (tt, J = 3.86, 3.82 Hz, 4 H), 2.42 (s, 1 H), 2.07 (t, J = 2.32 Hz, 1 H),1.82 (t, J = 4.48 Hz, 1 H) ppm. MS (FIA): m/z (%) = 764(20) [2 M – 4]$^+$, 663 (100). $C_{13}H_{20}OS_6$ (384.66): calcd. C 40.59, H 5.24; found C 40.67, H 5.26.

2-Pivaloyl-6-formylpterin Dimethyl Acetal (22): 2,5,6-Triaminopteridin-4(3*H*)-one hydrochloride (1 g, 4.2 mmol) was dissolved in H_2O (50 mL), and sodium sulfite (2 g) was added slowly for neutralization. Pale yellow 3,3-dimethoxy-2-oxopropanal (0.792 g, 6.1 mmol) was then added dropwise, and the mixture was stirred at room temperature for 12 h. The resulting slurry was centrifuged. The solid separated was filtered through a sintered funnel, washed well with H_2O and then with ethanol and dried in vacuo. The solid thus obtained was directly used for pivaloylation. The bright yellow semisolid **21** (600 mg, 54%), upon its pivaloylation with pivalic anhydride and a catalytic amount of DMAP followed by silica gel column chromatography, gave white crystals of **22** (500 mg, 71%). R_f = 0.7 (CH_2Cl_2/MeOH, 25:1); m.p. 118–119 °C. FT-IR (KBr): $\tilde{\nu}_{max}$ = 3480, 2971, 1697, 1621, 1158, 1073 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 12.75 (br. s, 1 H), 9.07 (s, 1 H), 8.92 (s, 1 H), 5.50 (s, 1 H), 3.50 (s, 3 H), 3.48 (s, 3 H), 1.35 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 180.9, 159.4, 158.1, 149.7, 141.7, 131.6, 103.9, 54.9, 40.6, 26.9 ppm. MS (ESI): m/z (%) = 643 (22) [2 M + H]$^+$, 322 (100) [M + H]$^+$. $C_{14}H_{19}N_5O_4$ (321.34): calcd. C 52.33, H 5.96, N 21.79; found C 52.40, H 6.00, N 21.74.

2-Pivaloyl-6-formylpterin (24): 2,5,6-Triaminopyridine-4(3*H*)-one hydrochloride (2 g.) was dissolved in H_2O (100 mL), and sodium sulfite (2 g) was added to the solution for neutralization (pH = 6). Pale yellow, liquid 2,2-dihydroxy-1,3-dipropanal (i.e the tricarbonyl compound) was added dropwise, and the reaction mixture was stirred at room temperature for 16 h. The resulting slurry was then centrifuged. The solid separated was then filtered through a sintered funnel, washed well with H_2O and then ethanol and finally with diethyl ether to leave a yellow powder **23** (860 mg, 55%). A slurry of **21** (1 g, 4.2 mmol) in HCl (10 mL, 1 N) was heated slowly in an oil bath to an external temperature of 110 °C and then cooled slowly to room temperature; when the solution reached 90 °C, most of the starting material had dissolved, and a bright yellow precipitate began to form. Upon cooling, the yellow solid was collected, washed with H_2O followed by ethanol and dried in vacuo to leave **23** (90 mg, 98%). This solid **23** (480 mg, 2.51 mmol) was directly used for pivaloylation. The solid yellow compound (480 mg), freshly distilled pivalic anhydride (5 mL) and 4-(dimethylamino) pyridine (DMAP, 50 mg) were heated at reflux for 6 h. A substantial amount of pivalic anhydride was distilled off with a short-path distillation apparatus. Column chromatography [elution with MeOH in chloroform (5%)] afforded **24** as a white crystalline solid (497 mg, 72%). To a stirred solution of **22** (400 mg, 1.5 mmol) in CH_2Cl_2 at room temperature was added TFA (0.5 mL) dropwise by syringe over 15 min. The solution was then reflux at 50–60 °C and stirred for a further 3 h. The solvent was evaporated in vacuo, the residue was azeotropically treated with Et_2O (3 × 10 mL) to remove residual TFA and purified by silica gel column chromatography eluting with MeOH/chloroform, which afforded **24** (315 mg, 92%) as a white crystalline solid. R_f = 0.4 (CH_2Cl_2/MeOH, 20:1); m.p. 246–247 °C (ref.[25] 247–248 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 12.52 (br. s, 1 H), 10.26 (s, 1 H), 9.40 (s, 1 H), 8.55 (br. s, 1 H), 1.36 (s, 9 H) ppm.

2-(Dimethoxymethyl)quinoxaline (26): To a solution of *o*-phenylenediamine (400 mg, 3.7 mmol) in dry ethanol (5 mL), which was stirred for 5–6 min, yellow, liquid **4a** (270 mg, 3.7 mmol) was added dropwise, and the reaction mixture was stirred at 70–80 °C for 3–4 h. The progress of the reaction was monitored by TLC. The ethanol was removed with a short-path distillation apparatus, and the crude material was purified by silica gel column chromatography eluting with petroleum ether/CH_2Cl_2 (1:1) to afford a pure, brown solid (600 mg, 85%). R_f = 0.6 (CH_2Cl_2/petroleum ether, 1:1); m.p. 85–86 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.10 (s, 1 H), 8.17–8.12 (m, 2 H), 7.80–7.77 (m, 2 H), 5.56 (s, 1 H), 3.50 (s, 6 H) ppm. MS (EI): m/z (%) = 174 (37) [M + H – OMe]$^+$. $C_{11}H_{12}N_2O_2$ (204.23): calcd. C 64.69, H 5.92, N 13.72; found C 64.69, H 5.99, N 13.80.

2-Quinoxalinecarbaldehyde (27): A mixture of **26** (320 mg, 1.56 mmol), formic acid (5 mL) and H_2O (3–4 drops) was added to

a round-bottomed flask. The reaction mixture was stirred at room temperature for 4–5 h and then neutralized with solid $NaHCO_3$. The H_2O layer was then extracted with EtOAc, and the solvent was evaporated to yield a white crystalline solid, which was purified by column chromatography on silica gel (100–200 mesh) eluting with petroleum ether/CH_2Cl_2 (3:2) to give a crystalline solid of **27** (160 mg, 94%). To a solution of *o*-phenylenediamine (500 mg, 4.6 mmol) in dry ethanol (5 mL), which was stirred for 5–6 min, a solution of **6a** (480 mg, 4.6 mmol) in ethanol (5 mL) was added dropwise, and the reaction mixture was stirred at 65–70 °C for 4 h. The progress of the reaction was monitored by TLC. The ethanol was removed with a short-path distillation apparatus, and the crude material was purified by silica gel column chromatography eluting with petroleum ether/chloroform (3:2) to afford a pure solid of **27** (670 mg, 92%). A mixture of **28** (200 mg, 0.66 mmol) and aqueous NaOH (2 N, 10 mL) was heated at 90 °C for 3 h. The consumption of the substrate was monitored by TLC. When all the substrate had been consumed, the reaction mixture was cooled and neutralized with solid $NaHCO_3$. The organic layer was extracted with CH_2Cl_2 (2×15 mL), washed with H_2O, dried (with Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with petroleum ether/chloroform (3:2) to give solid **27** (87 mg, 84%). R_f = 0.5 (CH_2Cl_2/petroleum ether, 1:1); m.p. 68–69 °C (ref.[18] 109 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.22 (s, 1 H), 9.36 (s, 1 H), 8.19 (d, J = 8.3 Hz, 1 H), 8.15 (d, J = 8.3 Hz, 1 H), 7.89–7.82 (m, 2 H) ppm. MS (FD): *m*/*z* (%) = 158 (100) $[M]^+$.

2-(Dibromomethyl)quinoxaline (28): *o*-Phenylenediamine (80 mg, 0.74 mmol), 3,3-dibromo-2-oxopropanal (210 mg, 1.39 mmol) and ethanol (10 mL) were mixed and then stirred at 70–80°°C for 6–8 h. The progress of the reaction was monitored by TLC. After 8 h, the ethanol was completely removed. H_2O was then added, and the organic product was extracted with chloroform and dried with Na_2SO_4. The compound was purified by preparative thin layer chromatography eluting with 2% EtOAc in petroleum ether to afford **28** as a brown crystalline solid (156 mg, 70%), followed by 2-quinoxalinecarbaldehyde (12 mg, 11%). R_f = 0.7 (CH_2Cl_2/petroleum ether, 1:3); m.p. 118–119 °C. FT-IR (KBr): $\tilde{\nu}_{max}$ = 2983, 1637, 1494, 1170, 767 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.39 (s, 1 H), 8.17–8.13 (m, 1 H), 8.08–8.04 (m, 1 H), 7.84–7.26 (m, 2 H), 6.77 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 177.0, 153.2, 144.9, 131.5, 131.4, 129.9, 129.6, 39.0, 30.0 ppm. MS (ESI): *m*/*z* (%) = 302 (80) $[M]^+$. $C_9H_6N_2$ (142.16): calcd. C 35.80, H 2.00, N 9.28; found C 35.92, H 2.11, N 9.36.

3-(Dimethoxymethyl)pyrido[2,3-*b*]pyrazine (30): To a solution of **29** (600 mg, 5.50 mmol) in dry ethanol (10 mL), which was stirred for 5–10 min, yellow, liquid **4a** (825 mg, 5.50 mmol) was added dropwise, and the reaction mixture was stirred at 70–80 °C for 3–4 h. The progress of the reaction was monitored by TLC. The ethanol was removed with a short-path distillation apparatus, and the crude material was purified by silica gel column chromatography eluting with MeOH in chloroform (2%) to afford **30** as a pure brown solid (950 mg, 85%). R_f = 0.4 (EtOAC/petroleum ether, 1:5); m.p. 142–144 °C (dec.). FT-IR (KBr): $\tilde{\nu}_{max}$ = 2918, 1485, 1456, 1103, 1067, 795, 772 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.18 (s, 1 H), 9.17 (t, J = 2.04 Hz, 1 H), 8.48 (dd, J = 1.72, 1.72 Hz, 1 H), 7.20 (dd, J = 4.20, 4.20 Hz, 1 H), 5.51 (s, 1 H), 3.53 (s, 6 H) ppm. MS (FIA): *m*/*z* (%) = 206 (100) $[M + H]^+$. $C_{10}H_{11}N_3O_2$ (205.10): calcd. C 58.53, H 5.40, N 20.48; found C 58.46, H 5.43, N 20.42.

Pyrido[2,3-*b*]pyrazine-3-carbaldehyde (31): To a solution of **29** (600 mg, 5.50 mmol) in dry ethanol (5 mL), which was stirred for 5–6 min, a solution of **6a** (570 mg, 5.50 mmol) in ethanol (5 mL) was added dropwise, and the reaction mixture was stirred at 65–70 °C for 4 h. The progress of the reaction was monitored by TLC. The ethanol was removed with a short-path distillation apparatus, and the crude material was purified by silica gel column chromatography eluting with MeOH in chloroform (4%) to afford pure solid **31** (500 mg, 57%). A mixture of 3-(dimethoxymethyl) pyrido[2,3-*b*]pyrazine (450 mg, 1.8 mmol), formic acid (5 mL) and H_2O (3–4 drops) were added to a round-bottomed flask. The reaction mixture was stirred at room temperature for 4–5 h and then neutralized with solid $NaHCO_3$. The H_2O layer was then extracted with EtOAc, and the solvent was evaporated to yield a white crystalline solid, which was purified by column chromatography on silica gel (100–200 mesh) eluting with MeOH in chloroform (2%) to give **31** as crystalline solid (286 mg, 82%). R_f = 0.25 (EtOAc/petroleum ether, 1:5); m.p. 91–93 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.39 (s, 1 H), 9.54 (s, 1 H), 9.21 (d, J = 7.29 Hz, 1 H), 8.50 (dd, J = 1.50, 1.50 Hz, 1 H), 7.77 (dd, J = 4.0, 4.0 Hz, 1 H) ppm.

Typical Experimental for the Synthesis of the Biheterocycles 32–36: *o*-Phenylenediamine (600 mg, 5.56 mmol) was dissolved in dry ethanol (20 mL). The smallest tetracarbonyl compound **16** (1.2 g, 0.0083 mol) or **18** (950 mg, 8.30 mmol) in ethanol (10 mL) was added dropwise to the reaction mixture over 15 min. The reaction mixture was heated at reflux for 4–5 h, the solvent was evaporated under reduced pressure, and the resulting brown gum was triturated with petroleum ether to yield a pale yellow solid. The solid was subjected to column chromatographic purification by eluting with 1% MeOH in CH_2Cl_2 to afford pure crystalline solid **33** (920 mg, 64%). The spectroscopic data and the yields of the compounds are mentioned below.

7,7′-Bi[2-(pivaloylamino)pteridin-4(3*H*)-one] (32): Yield 46%; yellow crystalline solid. R_f = 0.5 (CH_2Cl_2/MeOH, 20:1); m.p. >250 °C. FT-IR (KBr): $\tilde{\nu}_{max}$ = 3306, 2923, 1644, 1538, 1297, 1277, 1012, 738 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 12.23 (br. s, 1 H), 11.60 (br. s, 1 H), 8.65 (br. s, 2 H), 8.09 (s, 2 H), 1.45 (s, 9 H), 1.40 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 181.20, 159.36, 154.00, 153.16, 149.90, 137.73, 131.81, 52.39, 27.27 ppm. MS (FIA): *m*/*z* (%) = 526 (12) $[M - 2 + 2\ H_2O]^+$, 422(35) $[M - CMe_3]^+$, 363 (100). $C_{22}H_{24}N_{10}O_4$ (496.53): calcd. C 53.64, H 4.91, N 28.44; found C 53.72, H 4.97, N 28.36.

2,2′-Biquinoxaline (33): Yield 64%; off-white crystalline solid. R_f = 0.7 (EtOAC/petroleum ether, 1:5); m.p. 159–161 °C (dec.). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.11 (s, 2 H), 8.31–8.18 (m, 3 H), 7.92–7.82 (m, 3 H) ppm.

7,7′-Dimethoxy-3,3′-bi(pyrido[2,3-*b*]pyrazinyl) (34): Yield 57%; cream-colored solid. R_f = 0.45 (EtOAC/petroleum ether, 1:5); m.p. 145–148 °C. FT-IR (KBr): $\tilde{\nu}_{max}$ = 2916, 1337, 1310, 1212, 1220, 774 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.75 (s, 1 H), 9.63 (s, 1 H), 9.30 (d, J = 2.00 Hz, 2 H), 8.81 (d, J = 2.39 Hz, 1 H), 8.72 (d, J = 2.29 Hz, 1 H), 4.12 (s, 3 H), 4.10 (s, 3 H) ppm. MS (FIA): *m*/*z* (%) = 290 (36) $[M + H - OMe]^+$. $C_{16}H_{12}N_6O_2$ (320.10): calcd. C 60.00, H 3.78, N 26.24; found C 60.12, H 3.79, N 26.22.

3,3′-Bi(pyrido[2,3-*b*]pyrazinyl) (35): Yield 62%; cream-colored crystalline solid. R_f = 0.3 (EtOAC/petroleum ether, 1:5); m.p. 181–182 °C (dec.) FT-IR (KBr): $\tilde{\nu}_{max}$ = 2923, 2852, 1215, 1024, 763, 669 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.43 (s, 2 H), 9.32 (t, J = 1.86 Hz, 2 H), 8.64 (dd, J = 1.41, 1.50 Hz, 2 H), 7.86 (dd, J = 4.14, 4.14 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 155.2, 146.0, 138.8, 126.4 ppm. MS (FIA): *m*/*z* = 261 $[M + H]^+$ (100). $C_{14}H_8N_6$ (260.10): calcd. C 64.61, H 3.10, N 32.29; found C 64.53, H 3.12, N 32.36. Crystal data: Empirical formula $C_{28}H_{16}N_{12}$, formula mass 520.538, crystal system monoclinic, space group $P2_1/n$ (no. 14), cell parameters: a = 4.4766(3), b = 11.5709(7), c =

11.1346(7) Å, β = 195.328(4), V = 574.26(6) Å^3, Z = 1, D_c = 1.505 g/cm^3, μ(Mo-K_α) = 0.099 mm^{-1}, F(000) = 268, crystal size 0.25×0.28×0.49 mm, T = 100.0(1) K, λ(Mo-K_α) = 0.71073 Å, $\theta_{min/max}$ = 2.5/32.5°, total/unique data/R(int) = 8810/2081/0.023, observed data = 1760 [$I > 2.0\sigma(I)$], N_{ref} = 2081, N_{par} = 91, R = 0.0466, $wR2$ = 0.1412.

2,3′-Bi(pyrido[2,3-*b*]pyrazinyl) (36): Yield 22%; cream-colored crystalline solid. R_f = 0.35 (EtOAC/petroleum ether, 1:5); m.p. 210–214 °C. FT-IR (KBr): $\tilde{\nu}_{max}$ = 2901, 2821, 1209, 1047, 775, 670 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.47 (s, 1 H), 10.23 (s, 1 H), 9.29–9.26 (m, 2 H), 8.61 (dd, J = 8.40, 8.30 Hz, 2 H), 7.81 (dd, J = 3.96, 3.96 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 154.5, 136.8, 122.9, 115.0 ppm. $C_{14}H_8N_6$ (260.10): calcd. C 64.61, H 3.11, N 32.29; found C 64.33, H 3.19, N 32.38.

CCDC-638444 (for **8**), -638445 (for **10**), -684341 (for **12**), -638446 (for **15**) and -684340 (for **35**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.

Supporting Information (see also the footnote on the first page of this article): General experimental method, a description of how X-ray data were collected, ^{1}H NMR spectra, and other characterization data for all new compounds **4a**, **6a**, **7**, **8**, **9**, **10**, **11**, **12**, **15**, **19**, **22**, **24**, **26**, **28**, **30**, **32**, **34**, **35** and **36**; selected crystallographic data of **8**, **10**, **12**, **15** and **35**.

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