even at 500 MHz reduce the use of 1D kinetic NOE experiments, (2) because $\omega\tau_c \approx 1$, many NOESY cross peaks would be expected to be small or lost entirely, (3) spin diffusion is not as significant in molecules for which τ_c is short, and (4) relatively long relaxation times allow for longer linear ROESY buildup observation. The ROESY buildup rates led to more reliable cross-peak volumes, and thus internuclear proton–proton distances because nonlinear buildup rates and peaks opposite in sign to the diagonal ruled out false NOE interactions.

ROESY spectra were obtained nonspinning at 27 °C in $CDCl_3$ solution using a Kessler spin lock of 30° pulses, States–Haberkorn phase cycling, and arraying the mixing time of the spin lock over the range 50–175 ms. Homospoil irradiation and a recycle delay of 3.4–5 s were employed. From three to six mixing times were used in each experiment. Estimations of initial buildup rates of individual cross peaks were made by volume integration of cross peaks (the integral scale of each spectrum set to a consistent, arbitrary value), and by linear least-squares fit of the volumes versus mixing time to a straight line. Calculation of proton–proton distances were then made under the assumption that the initial buildup rate was proportional to r_{ab}^{-6} where r_{ab} is the proton–proton internuclear distance; a fundamental distance reference was obtained by assigning the geminal CH_2 proton–proton distance for all aliphatic CH_2 pairs in the molecule to 1.8 Å.

1D NOE's were obtained in acetonitrile solution by interleaving the collection of spectra in which either an off-resonance or on-resonance presaturation with $\gamma H_2 \approx 40$ Hz for 3 s was followed with an observed 90° pulse (total recycle delay = 7 s); difference spectroscopy then provided the results.

Acknowledgment. The authors wish to thank T. Adams and A. Vatakis for their assistance in the isolation, Dr. C. Metral for providing high-resolution mass spectra, and G. N. McGregor of the Biomedical Supercomputing Center at this facility for writing programs to handle assignments from large 1D and 2D data sets. Research sponsored by the National Cancer Institute, DHHS, under Contract No. N01-CO-74102 with PRI/DynCorp. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

Supplementary Material Available: Complete tables of ^1H (500-MHz) and ^{13}C (125-MHz) NMR assignments in $CDCl_3$ and IR, UV, and HR FABMS data for bryostatin 3 (1) and 20-*epi*-bryostatin 3 (2) (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

New Analogs of *cyclo*(Prn-Prn): Synthesis of Unsymmetric Octahydro-1*H*,5*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-5,10-diones

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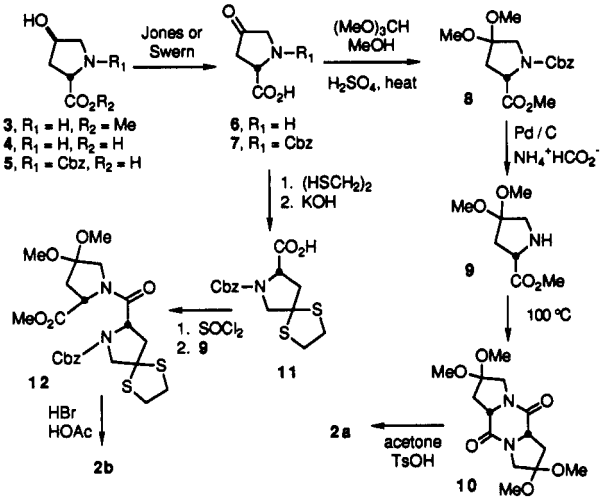
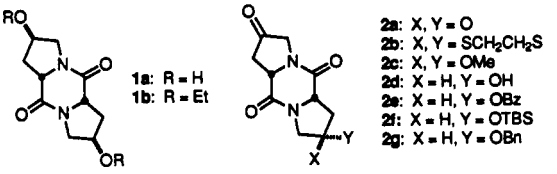
Received February 10, 1992 (Revised Manuscript Received June 18, 1992)

Synthesis of *trans*-4-hydroxy-L-proline cyclic dimer (**1a**, *cyclo*(Hyp-Hyp)) was first achieved by Kapfhammer and Matthes in 1933 and again in the 1970's by three other groups.[2-6] The only published derivatives of **1a** are *O*-ethyl ether **1b** and 4-oxo-L-proline cyclic dimer **2a** (*cyclo*(Prn-Prn)).[6-9] The highly symmetric, highly functionalized **2a** is an inviting framework for constructing conformationally restricted analogs of potential biological interest. In addition to a new preparation of **2a**, we report synthetic routes effectively differentiating the homotopic carbonyls and allowing for selective synthesis of congeners masking the C_2 symmetry.

Scheme I





Initially, we anticipated that **2a** would provide us with a readily available base of operations for our proposed derivatizations. Although ample supplies of **1a** were available by dimerization of *trans*-4-hydroxy-L-proline methyl ester (**3**),[2] we were unable to consistently reproduce the yield reported for DMSO/DCC oxidation to **2a**.[6] Furthermore, the long reaction time (5 days), low solubility of **2a** in most organic solvents (1 g/2000 mL of acetone), and the "extensive purification" required with this method discouraged our plans for scale up. A variety of other methods investigated for **1a** → **2a** conversion including DMSO/$(COCl)_2$,[10] DMSO/TFAA, DMSO/SO_3/pyr, DMSO/DCC/TFA/pyr, Jones reagent,[11] CrO_3/IRA400/DMF,[12] PCC/DMF, PCC/Al_2O_3,[13] and RuO_4[14-16] were

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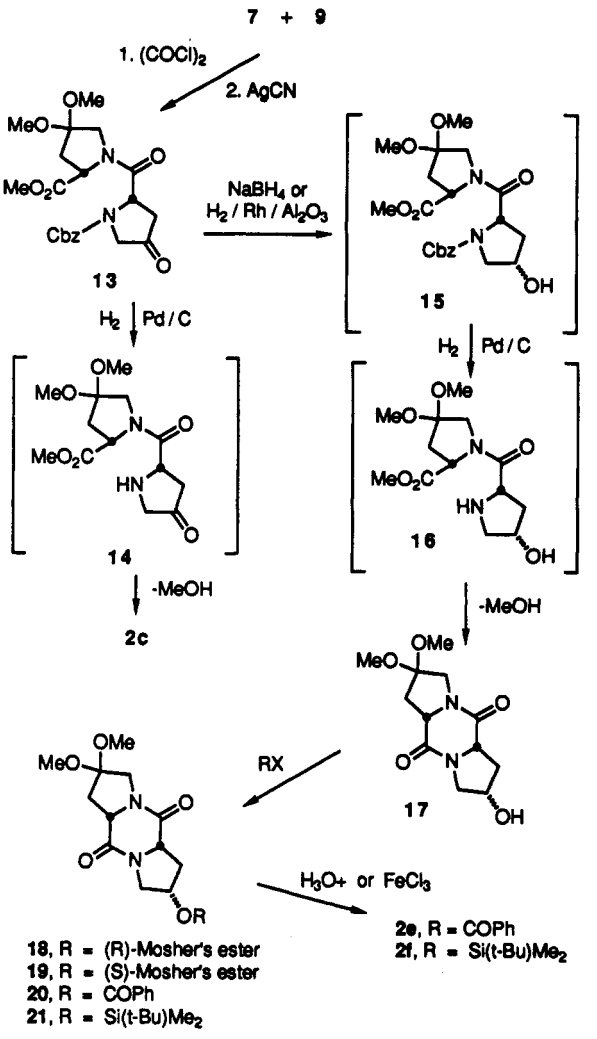
unsuccessful. In most cases, the disappearance of diol **1a** (TLC) was not followed by the reappearance of dione **2a**. The boat conformation of the diketopiperazine ring and the overall cupped shape of this fused ring system are clearly depicted in molecular models of **1a** and the X-ray structure of *cyclo*(Pro-Hyp),[17] but there is little indication of unusual steric or electronic factors that might impede the reaction.

If the difficulties with oxidation of **1a** are a consequence of its unique topology, then oxidation of the alcohol should *precede* dimerization. Although the HBr salt of 4-oxo-L-proline (**6**) is available by Jones oxidation of *trans*-4-hydroxy-L-proline (**4**), the free base is prone to oligomerization via aldol condensation and elimination.[18] *N*-Cbz-*trans*-4-hydroxy-L-proline (**5**) is also oxidized to ketone **7** with either Jones[18] or Swern conditions (Scheme I).[10,19] Both procedures give similar yields, but there is greater variability in yield and purity of **7** using Jones' reagent than **7** produced by Swern oxidation. Protection of **7** as ketal ester **8** in one step using a variation of the previously reported two-step process and removal of the *N*-Cbz gives amine **9**.[20] Amine **9** dimerizes slowly to **10** on standing at room temperature, but this reaction can be hastened by heating the neat oil in a vacuum oven. When **10** is treated with TsOH/acetone, dione **2a** precipitates and is isolated by filtration in 30% yield from **9**.

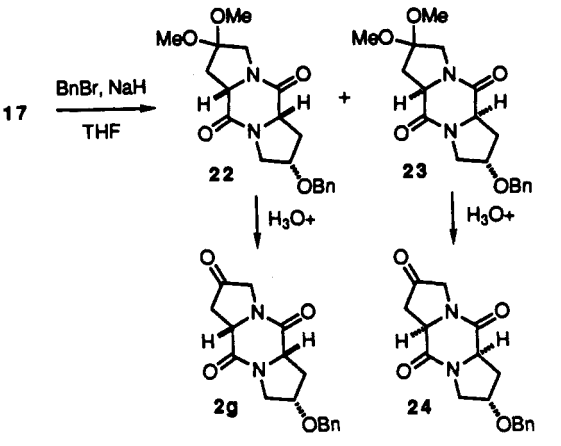
This preparation of **2a** from **5** is more reliable than the previously reported method and provides important clues contributing to the successful synthesis of masked equivalents of **2a**. In fact, moving the Swern reaction to an earlier point in the synthesis not only solves the oxidation problem but also enables differentiation of the ketones. Ketone **7** is first protected as dithiolane **11** (Scheme I).[21-23] Activation as the acid chloride followed by coupling with amine **9** gives dipeptide **12**, and N-deprotection with HBr/HOAc leads to thioketal **2b**. This method is adequate for the preparation of small quantities of **2b** (<1 g), but difficulties encountered during attempted scale up (>10 g) suggest that its practical application would be problematic. For example, thioketalization of **7** is inevitably accompanied by partial thioesterification, and comparatively harsh conditions for N-deprotection (HBr/HOAc) of **12** are required. Furthermore, **2b** is reasonably soluble in DMF and DMSO, but is insoluble in most other common organic solvents, thereby limiting the range of reagents and conditions available for subsequent transformations.

Refinement of the **7** → **2b** sequence gives additional analogs of **2a**. Coupling acid **7** with amine **9** under mild conditions (oxalyl chloride/AgCN)[24-26] affords dipeptide

Scheme II



Scheme III



13 (Scheme II). Initial attempts to N-deprotect and cyclize **13** with standard hydrogenolysis methods (10% Pd/C/H_2) give only low yields of **2c** (<10%). Alternatively, 5% Rh/Al_2O_3/H_2 stereoselectively produces alcohol **17** in about 50% yield. Whereas deprotection of **13** with Pd/C/H_2 gives unstable amino ketone **14** as a reactive intermediate, treating **13** with Rh/Al_2O_3/H_2 apparently reduces the ketone at a rate competitive with benzyl cleavage (**13** → **15** → **16**) generating **17** in good yield. The

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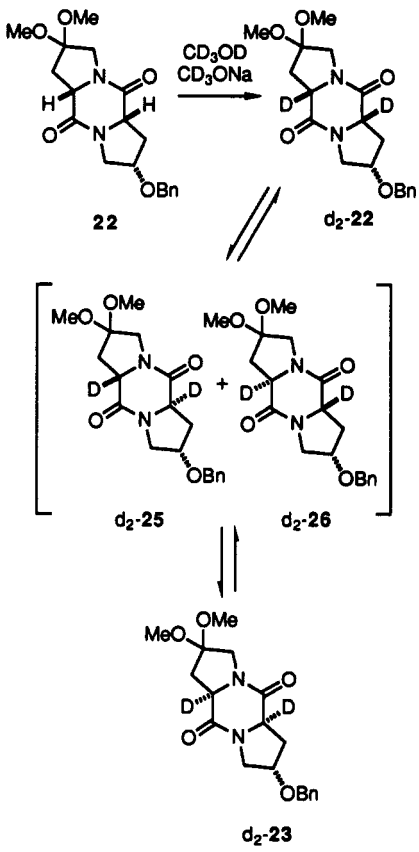
Scheme IV



preparation of **17** by this route is improved by reduction of **13** with $NaBH_4/Al_2O_3$, filtration, and hydrogenolysis ($Pd/C/H_2$) of the filtrate. Although borohydride reduction product **15** can be isolated, direct conversion of **17** is usually preferred. The stereochemical integrity of **17** was measured by examination of (*R*)- and (*S*)-Mosher's esters **18** and **19**. The isomeric purities of **18** and **19** are at least 97% by HPLC, indicating that the 5a*S*,10a*S* configuration is preserved and the $NaBH_4/Al_2O_3$ reduction (**13** → **15**) is highly stereoselective. Thus, ketal **17** is prepared in five steps and 16% yield from **5**. Hydrolysis of ketal **17** produces water-soluble, hygroscopic ketone **2d**. Esterification affords benzoate **20** and hydrolysis generates **2e**. Single-crystal X-ray diffraction of **20** confirms the 2*S*,5a*S*,10a*S* configuration.[17] Similarly, silation of **17** and hydrolysis of **21** with freshly prepared $FeCl_3/SiO_2$ gives **2f** in good yield.[27]

Treating **17** with benzyl bromide/NaH gives a 1:1 mixture of the expected benzyl ether **22** and diastereomer **23** (Scheme III). Alkylation using $BnBr/Ag_2O/DMF$[28] gives only low yields of **22**, and other reagents such as BnOTf[29] and $Cl_3CC(=NH)OBn/TfOH$[30] were employed without success. Chromatographic separation of **22** and **23** and hydrolysis gives ketones **2g** and **24**, respectively. Closer examination of the benzylation by ^1H NMR suggests that the equilibrium between **22** and **23** is catalyzed by the sodium alkoxide of **17**. For example, **22** is recovered unchanged when resubjected to Na/THF; **23** is also unaffected. However, when **22** is treated with CD_3OD/CD_3ONa the methine H's are rapidly exchanged with *retention of configuration* in less than 5 min by ^1H NMR (Scheme IV). After standing at ambient temperature, the sample equilibrates to a 1:1 mixture of **22**-d_2 and **23**-d_2. Trans isomers are not detected, but they probably form as short-lived intermediates on a high-energy plateau along the equilibrium pathway between **22**-d_2 and **23**-d_2. The benzyloxy substituent is able to occupy a pseudoequatorial position in both **22** and **23** via envelope flip and does not affect the cis/trans ratio. These observations are consistent with earlier reports that the trans isomers of *cyclo*(Pro-Pro) and *cyclo*(Hyp–Hyp) rapidly isomerize to the cis isomers with alkoxide.[3,4,31]

Summary/Conclusions. Until recently, synthetic access to the symmetric scaffolding of the octahydro-1*H*,5*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-5,10-dione ring system has been limited. Now, however, new syntheses of *cyclo*(Prn-Prn) (**2a**) and monoprotected analog **2b** are available. Modification of these routes produces hydroxy ketal **17** in five steps (**5** → **7** → **8** → **9** → **13** → **17**), 16% overall yield, and at least 97% de from commercially available **5**. Ketal **17** is the key intermediate used to prepare analogs **2e,f,g** in which the C_2 symmetry of **2a** is masked. Extension of this methodology may be useful for constructing additional analogs of potential biological interest.

Experimental Section

General. All reagents and solvents were used as received from commercial sources without further purification unless otherwise noted. Melting points are uncorrected. THF was distilled from sodium/benzophenone immediately prior to use. Organic extracts were dried with anhydrous $MgSO_4$. Medium-pressure liquid chromatography (MPLC) was performed with a Büchi 681 pump using heavy-glass columns (25-, 50-, or 75-mm diameter, 460-mm long) packed with E. M. Science silica gel 60 (40–63 μm, 230–400 mesh) and solvent flow rates of 20–35 mL/min. NMR spectra were recorded on a GE QE-300 instrument at 300 (^1H) and 75 MHz (^{13}C). *J* values are given in Hz. IR data given in cm^{-1}.

(5a*S*,10a*S*)-Octahydro-2,2,7,7-tetramethoxy-1*H*,5*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-5,10-dione (10). Amino ester **9** (2.7 g) was placed in a vacuum oven at 200–300 Torr and 100 °C for 72 h. The solid, black residue was dissolved in 100 mL of EtOAc, stirred with charcoal for 45 min, filtered through Celite, and evaporated to give 0.66 g of a yellow solid. The crude product was filtered through a plug of silica gel with EtOAc and evaporated to give 0.57 g (26%) of **10**: mp 144–146 °C; IR (KBr) 1654; ^1H NMR ($CDCl_3$) δ 2.38 (1, dd, *J* = 13.1, 9.5), 2.50 (1, dd, *J* = 13.2, 7.5), 3.26 (3, s), 3.27 (3, s), 3.59 (1, d, *J* = 12.2), 3.66 (1, d, *J* = 12.2), 4.31 (1, t, *J* = 8.4); ^{13}C NMR ($CDCl_3$) δ 35.2, 49.3, 50.4, 51.3, 58.4, 106.0, 165.9; FAB MS 315 (MH^+), 283 (MH – MeOH), 251 (MH – 2MeOH). Anal. Calcd for $C_{14}H_{22}N_2O_6$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.41; H, 6.98; N, 8.74.

(5a*S*,10a*S*)-Octahydro-1*H*,5*H*-dipyrrolo[1,2-*a*:1′,2′-*d*]-pyrazine-2,5,7,10-tetrone (2a). Amino ester **9** (12.4 g) was placed in a vacuum oven at 200–300 Torr and 100 °C for 72 h. The solid, black residue (**10**) was dissolved in 100 mL of acetone with 4 g of $TsOH\cdot H_2O$ at 23 °C for 48 h. The white precipitate was collected on a Büchner funnel, washed with acetone and ether, and dried in vacuo to give 2.34 g (32%) of **2a**. IR, ^1H NMR, EI MS, HRMS, $[\alpha]_D$, and combustion analysis have been reported:[6] ^{13}C NMR (DMSO-d_6) δ 53.1, 57.4, 57.5, 166.4, 208.4.

7-[(Phenylmethoxy)carbonyl]-1,4-dithia-7-azaspiro[4.4]-nonane-8(*S*)-carboxylic Acid (11). A solution of 5.78 g (22 mmol) of **7** and 4.6 mL (22 mmol) of 1,2-ethanedithiol in 55 mL of $CHCl_3$ was stirred with 2.5 g of Amberlyst-15 at ambient temperature for 48 h.[21] The mixture was filtered, the filtrate was concentrated, and the residue was taken up in 80 mL of methanol and 80 mL of 1 M NaOH. After 3 h, the solution was acidified to pH 1 with 1 M H_2SO_4, concentrated to approximately 100 mL, and extracted with $CHCl_3$ (3×). The combined organic layers were washed with brine (1×), dried, filtered, treated with charcoal,

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filtered, and evaporated to give 6.88 g (95%) of 11.[22,23]

(5aS,10aS)-Octahydro-1H,5H-dipyrrolo[1,2-a:1',2'-d]pyrazine-2,5,7,10-tetrone, 2,2-Ethylene Dithioketal (2b). A solution of 4.38 g (12.9 mmol) of 11 in 20 mL of thionyl chloride was stirred at 23 °C for 4 h. The excess solvent was evaporated and the residue dissolved in 30 mL of dry THF and treated with 2.44 g (12.9 mmol) of 9 and 1.65 mL (15 mmol) of *N*-methylmorpholine. After being stirred for 17 h, the mixture was diluted with EtOAc and washed with 1 M HCl (3×) and saturated $NaHCO_3$ (3×), dried, filtered, and evaporated to give 5.37 g of a foamy residue (12) which was dissolved in 50 mL of glacial acetic acid and treated with 25 mL of HBr/HOAc. After 60 min at 23 °C, the solution was diluted with Et_2O, the supernatant was decanted away from the precipitate (ppt), and the ppt was washed with more Et_2O (3×). The solid remaining was dissolved in 100 mL of MeOH and treated with 50 g of AG3-X4 ion-exchange resin without stirring for 16 h. The mixture was filtered and evaporated to give 2.52 g (81%) of a yellow solid. The crude product was boiled with 200 mL of acetone, the heterogeneous mixture was filtered (hot), the filtrate cooled to room temperature, and the precipitate collected on a Büchner funnel and dried in vacuo to give 1.06 g (34%) of **2b**: mp 248–250 °C; IR (KBr) 1764, 1690, 1667; ^1H NMR ($CDCl_3$) δ 2.78 (2, d, J = 8.1), 2.90 (1, dd, J = 19.5, 9.1), 3.14 (1, ddd, J = 19.3, 9.5, 0.9), 3.4 (4, m), 3.79 (1, d, J = 19.7), 3.90 (1, d, J = 12.6), 4.00 (1, d, J = 12.5), 4.14 (1, d, J = 19.7), 4.48 (1, t, J = 7.9), 4.66 (1, t, J = 9.0); ^{13}C NMR (DMSO-d_6) δ 38.5, 38.9, 42.6, 51.8, 56.5, 58.8, 59.3, 65.2, 164.7, 165.3, 207.0; CI MS 299 (MH^+). Anal. Calcd for $C_{12}H_{14}N_2O_3S_2$: C, 48.31; H, 4.73; N, 9.39; S, 21.49. Found: C, 48.10; H, 4.76; N, 9.22; S, 21.79.

4,4-Dimethoxy-1-[4-oxo-1-[(phenylmethoxy)carbonyl]-(S)-prolyl]-(S)-proline, Methyl Ester (13). A solution of 18.2 g (69.0 mmol) of 7 and 30.0 mL (345 mmol) of oxalyl chloride in 365 mL of benzene (dried over 4A molecular sieves) was heated to reflux for 4 h. After the solution was cooled to room temperature, the solvent was evaporated. Residual HCl was removed by dissolving the oily product in 300 mL of benzene and evaporating (3×). The crude acid chloride was dissolved in 100 mL of toluene and added to a suspension of 13.0 g (69.0 mol) of amine 9 and 18.5 g (138 mmol) of AgCN in 120 mL of toluene.[24-26] The mixture was stirred at room temperature for 2–24 h and filtered through Celite. The filtrate was washed with saturated $NaHCO_3$ (3×) and brine (1×), dried, filtered, and evaporated. The gummy residue was filtered through a plug of silica gel, eluting first with hexane followed by 60:40 EtOAc–hexane. Evaporation of the second filtrate gave 22.6 g (75%) of 13. This product was normally used directly for the next reaction. Interpretation of the ^1H NMR spectrum was complicated by the presence at least two stable conformations at ambient temperature (supplementary material): IR (film) 1765, 1710, 1662; FAB MS 435 (MH^+), 403 (MH – MeOH), 338, 289, 248, 193; CI MS 403 (MH – MeOH); HR FAB calcd for $C_{20}H_{22}N_2O_7$ (MH – MeOH) 403.1505, found 403.1502.

(2S,5aS,10aS)-Octahydro-2-hydroxy-7,7-dimethoxy-1H,5H-dipyrrolo[1,2-a:1',2'-d]pyrazine-5,10-dione (17). A solution of ketone 13 (15.7 g, 36 mmol) in 360 mL of MeOH was chilled in an ice bath, and 10% $NaBH_4/Al_2O_3$ (4.7 g, 12 mmol) was added slowly. After 1 h at 23 °C, the suspension was filtered and the filtrate concentrated to ca. 280 mL by rotary evaporation. A slurry of 10% Pd/C (6.0 g catalyst/20–30 mL water) was added and the mixture treated with 50 psi of H_2 on a Parr apparatus for 9 h. The reaction mixture was filtered through Celite and evaporated. Due to the aqueous solubility of 17, excess water was removed by repeated azeotropic distillation with $CHCl_3$ (3 × 300 mL) on a rotary evaporator. The residue was taken up in $CHCl_3$ once more, dried, filtered, and evaporated to give 8.88 g of a sticky solid after removal of residual solvent in vacuo. Recrystallization from ca. 10 mL of EtOAc and washing with 1:1 EtOAc–hexane and Et_2O gave 5.42 g (56%) of 17: mp 110.5–112.5 °C; IR (film) 3420, 1668; ^1H NMR ($CDCl_3$) δ 2.25–2.40 (2, m), 2.40–2.60 (2, m), 3.20 (3, s), 3.22 (3, s), 3.34 (1, dd, J = 12.2, 4.3), 3.49 (1, d, J = 12.2), 3.62 (1, d, J = 12.0), 3.73 (1, bd, J = 12.2), 4.15 (1, dd, J = 8.9, 5.0), 4.29 (1, bt, J = 8.5), 4.42 (1, m); ^{13}C NMR ($CDCl_3$) δ 34.9, 35.3, 49.1, 50.4, 51.0, 53.0, 58.1, 58.5, 68.4, 105.9, 166.3, 166.4; CI MS 270, 239; FAB MS: 271, 239; HR FAB calcd for $C_{12}H_{19}N_2O_5$ (MH^+) 271.1294, found 271.1280.

(2S,5aS,10aS)-Octahydro-2-hydroxy-7,7-dimethoxy-1H,5H-dipyrrolo[1,2-a:1',2'-d]pyrazine-5,10-dione, Benzoate Ester (20). A solution of 2.11 g (7.81 mmol) of alcohol 17 in 30 mL of pyridine (previously dried over 4A molecular sieves) was chilled in an ice bath and treated with 3.6 mL (31 mmol) of benzoyl chloride. After 45 min, the solution was diluted with EtOAc and washed with water (1×), saturated $CuSO_4$ (3×), and saturated $NaHCO_3$ (2×). The organic layer was dried, filtered, and evaporated to give an oil which solidified on standing. The tan solid was washed with Et_2O (4×) and dried in vacuo to give 2.30 g (79%) of 20. An analytical sample was prepared by recrystallization from *i*-PrOAc; mp 145–148 °C; IR (KBr) 1717, 1677; ^1H NMR ($CDCl_3$) δ 2.4–2.7 (3, m), 2.94 (1, bd, J = 14), 3.21 (3, s), 3.27 (3, s), 3.60 (1, d, J = 11), 3.62 (1, m), 3.66 (1, d, J = 11.8), 4.10 (1, bd, J = 13.0), 4.33 (1, dd, J = 9.4, 4.5), 4.39 (1, t, J = 8.1), 5.50 (1, m), 7.40 (2, t, J = 7.7), 7.54 (1, t, J = 7.4), 7.92 (2, d, J = 7.3); ^{13}C NMR ($CDCl_3$) δ 32.6, 34.4, 49.4, 50.1, 51.1, 51.2, 57.9, 58.4, 71.5, 106.8, 128.2, 129.3, 129.5, 133.1, 165.5, 165.6, 165.2; CI MS 343 (MH – MeOH), 252 (MH – $PhCO_2H$), 220 (MH – MeOH – $PhCO_2H$). Anal. Calcd for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.98; N, 7.48. Found: C, 60.98; H, 5.85; N, 7.40.

(2S,5aS,10aS)-Octahydro-2-hydroxy-1H,5H-dipyrrolo-[1,2-a:1',2'-d]pyrazine-5,7,10-trione, Benzoate Ester (2e). A solution of 0.40 g (1.1 mmol) of 20 in 5 mL THF, 5 mL water, and 0.5 mL of 3 M H_2SO_4 was heated to 70 °C for 45 min. The solution was cooled to room temperature and extracted with EtOAc (3×). The combined organic layers were washed with saturated $NaHCO_3$ (1×) and brine (1×), dried, filtered, and evaporated to give 0.35 g (100%) of **2e**. An analytical sample was prepared by recrystallization from EtOAc: mp 200–202 °C dec; IR (KBr) 1777, 1719, 1656; ^1H NMR ($CDCl_3$) δ 2.72 (1, ddd, J = 14.6, 9.3, 5.3), 2.90–3.05 (2, m), 3.21 (1, dd, J = 19.8, 8.8), 3.73 (1, dd, J = 13.2, 4.9), 3.84 (1, d, J = 19.7), 4.12 (1, d, J = 19.6), 4.15 (1, bd, J = 13.2), 4.44 (1, dd J = 9.2, 4.9), 4.72 (1, t, J = 9.0), 5.56 (1, m), 7.43 (2, t, J = 7.6), 7.58 (1, tt, J = 7.3, 1.2), 7.93 (2, dd, J = 7, 1); ^{13}C NMR ($CDCl_3$) δ 32.9, 38.8, 51.5, 52.1, 57.3, 58.0, 71.4, 128.4, 129.3, 129.6, 133.4, 165.3, 165.7, 166.1, 205.8; CI MS 329 (MH^+), 206 (MH – $PhCO_2H$). Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 61.77; H, 4.83; N, 8.37.

(2S,5aS,10aS)-Octahydro-2-hydroxy-7,7-dimethoxy-1H,5H-dipyrrolo[1,2-a:1',2'-d]pyrazine-5,10-dione, O-(tert-Butyldimethylsilyl) Ether (21). A solution of 17 (2.0 g, 7.4 mmol), imidazole (0.76 g, 11 mmol), and *tert*-butyldimethylsilyl chloride (1.45 g, 9.62 mmol) in 10 mL of CH_2Cl_2 was stirred at 23 °C for 18 h. The solution was diluted with CH_2Cl_2, washed with water (3×) and brine (1×), dried, filtered, and evaporated. Removal of residual volatile silanes by evaporation in vacuo (0.1 Torr, 24–60 h, 23 °C) gave 2.52 g (88%) of a pale yellow solid. MPLC with 80:20 EtOAc–hexane gave 2.01 g (70%) of 21: mp 133–135 °C; IR (KBr) 1690, 1653; ^1H NMR ($CDCl_3$) δ 0.05 (3, s), 0.07 (3, s), 0.84 (9, s), 2.3–2.5 (4, m), 3.26 (6, s), 3.46 (1, dd, J = 11.8, 5.3), 3.54 (1, d, J = 12.1), 3.61 (1, dd, J = 11.9, 4.2), 3.67 (1, d, J = 12.3), 4.16 (1, t, J = 7.5), 4.31 (1, t, J = 8.4), 4.41 (1, m); ^{13}C NMR ($CDCl_3$) δ −5.15, −5.05, 17.6, 25.4, 35.1, 36.3, 49.1, 50.2, 51.2, 53.2, 58.1, 58.4, 69.1, 106.0, 165.9, 166.1; CI MS 385 (trace), 369, 353, 327. Anal. Calcd for $C_{18}H_{32}N_2O_5Si$: C, 56.22; H, 8.39; N, 7.28. Found: C, 56.33; H, 8.39; N, 7.18.

(2S,5aS,10aS)-Octahydro-2-hydroxy-1H,5H-dipyrrolo-[1,2-a:1',2'-d]pyrazine-5,7,10-trione, O-(tert-Butyldimethylsilyl) Ether (2f). A solution of 3.44 g (8.94 mmol) of 21 in 35 mL of acetone was treated with 3.0 g of $FeCl_3$ on silica gel for 5.5 h at 23 °C.[27] The suspension was filtered through Celite with EtOAc, and the filtrate was washed with water (3×) and brine (1×), dried, filtered, and evaporated to give 1.58 g (52%) of ketone 2f. An analytical sample was prepared by recrystallization from EtOAc/hexane: mp 143–145 °C; IR (KBr) 1767, 1675, 1661, 1647; ^1H NMR ($CDCl_3$) δ 0.09 (3, s), 0.10 (3, s), 0.80 (9, s), 2.39 (1, ddd, J = 13, 8.6, 4.4), 2.55 (1, m), 2.91 (1, dd, J = 19.4, 8.8), 3.16 (1, dd, J = 19.4, 9.2), 3.47 (1, dd, J = 11.8, 4.8), 3.73 (1, dd, J = 11.9, 3.2), 3.80 (1, d, J = 19.7), 4.09 (1, d, J = 19.7), 4.28 (1, bt, J = 7), 4.44 (1, m), 4.64 (1, t, J = 9.0); ^{13}C NMR ($CDCl_3$) δ −5.0, −4.9, 17.8, 25.5, 36.6, 39.2, 52.2, 53.9, 57.2, 58.1, 69.1, 165.4, 166.4, 205.9; CI MS: 339, 323, 281. Anal. Calcd for $C_{16}H_{26}N_2O_4Si$: C, 56.78; H, 7.74; N, 8.28. Found: C, 56.61; H, 7.78; N, 8.14.

(2S,5aS,10aS)- and (2S,5aR,10aR)-Octahydro-2-hydroxy-7,7-dimethoxy-1H,5H-dipyrrolo[1,2-a:1',2'-d]-pyrazine-5,10-dione, O-Benzyl Ethers (22 and 23). A solution of 5.45 g (20.2 mmol) of alcohol 17 in 60 mL of THF under N_2

was treated with 1.6 g of NaH (40.3 mmol) at 23 °C for 30 min, at which time 0.74 g (2.0 mmol) of Bu_4NI and 3.6 mL (30.2 mmol) of BnBr were added.[32] After 60 min, the reaction was carefully quenched with water and saturated NH_4Cl and extracted with EtOAc (2×). The organic phase was washed with water (2×) and brine (1×), dried, filtered, and evaporated. The products were separated by MPLC with 95:5 EtOAc–EtOH to give **22** (1.88 g, 26%, R_f = 0.41) and **23** (1.76 g, 24%, R_f = 0.54).

22: oil; IR (film) 1672; ^{1}H NMR ($CDCl_3$) δ 2.4 (2, m), 2.49 (1, dd, J = 13.2, 7.4), 2.71 (1, dt, J = 13.5, 5.2), 3.24 (3, s), 3.25 (3, s), 3.45 (1, dd, J = 12.3, 5.2), 3.56 (1, d, J = 12.2), 3.66 (1, d, J = 12.2), 3.87 (1, dd, J = 12.3, 2.9), 4.2 (2, m), 4.32 (1, t, J = 8.4), 4.44 (1, d, J = 11.9), 4.54 (1, d, J = 11.8), 7.3 (5, m); ^{13}C NMR ($CDCl_3$) δ 32.0, 34.6, 48.9, 50.0, 50.3, 50.7, 57.7, 58.1, 70.2, 74.6, 105.6, 127.2, 127.3, 127.9, 137.2, 165.6, 165.8; CI MS 361 (trace), 360 (trace), 329, 222; FAB MS 361, 329; HR FAB calcd for $C_{19}H_{24}N_2O_5$ 361.1763, found 361.1707.

23: mp 92–94 °C; IR (KBr) 1667; ^{1}H NMR ($CDCl_3$) δ 2.14 (1, ddd, J = 13, 11, 4.4), 2.36 (1, dd, J = 13.2, 9.4), 2.45–2.65 (2, m), 3.26 (6, s), 3.57 (1, d, J = 12), 3.63 (2, m), 3.73 (1, d, J = 13), 4.22 (1, t, J = 4.2), 4.35 (1, t, J = 8.4), 4.45 (1, dd, J = 10.9, 6.5), 4.53 (2, s), 7.35 (5, m); ^{13}C NMR ($CDCl_3$) δ 33.8, 34.9, 49.2, 50.2, 51.0, 51.1, 58.3, 58.7, 70.6, 75.3, 105.9, 127.4, 127.7, 128.3, 137.2, 165.4, 166.4; CI MS 361 (trace), 360, 329. Anal. Calcd for $C_{19}H_{24}N_2O_5$: C, 63.32; H, 6.71; N, 7.77. Found: C, 62.88; H, 6.57; N, 7.46.

(2*S*,5a*S*,10a*S*)-Octahydro-2-hydroxy-1*H*,5*H*-dipyrrolo-[1,2-*a*:1′,2′-*d*]pyrazine-5,7,10-trione, *O*-Benzyl Ether (2g). A solution of 1.95 g (5.41 mmol) of **22** in 25 mL of THF was treated with 25 mL of water and two drops of concd H_2SO_4 and heated to reflux for 1 h. The solution was cooled and extracted with EtOAc (3×), and the organic layers were washed with saturated $NaHCO_3$ (3×) and brine (1×), dried, filtered, and evaporated to give 1.18 g (60%) of ketone **2g**: mp 166–167 °C; IR (KBr) 1768, 1675, 1656; ^{1}H NMR ($CDCl_3$) δ 2.42 (1, ddd, J = 18.6, 9.1, 5.0), 2.8 (1, m), 2.89 (1, dd, J = 19.7, 9.1), 3.16 (1, dd, J = 19.5, 9.2), 3.46 (1, dd, J = 12.4, 4.9), 3.79 (1, d, J = 19.7), 3.98 (1, bd, J = 12.4), 4.11 (1, d, J = 19.7), 4.18 (1, m), 4.29 (1, dd, J = 9.0, 5.3), 4.45 (1, d, J = 11.9), 4.55 (1, d, J = 11.9), 4.64 (1, t, J = 9.0), 7.3 (5, m); ^{13}C NMR ($CDCl_3$) δ 32.8, 39.2, 51.4, 52.2, 57.3, 58.1, 70.9, 74.8, 127.8, 127.9, 128.5, 137.5, 165.2, 166.4, 205.8; FAB MS 315 (MH^+); HR FAB calcd for $C_{17}H_{19}N_2O_4$ (MH^+) 315.1345, found 315.1338.

(2*S*,5a*R*,10a*R*)-Octahydro-2-hydroxy-1*H*,5*H*-dipyrrolo-[1,2-*a*:1′,2′-*d*]pyrazine-5,7,10-trione, *O*-Benzyl Ether (24). A solution of 0.88 g (2.44 mmol) of **23** in 15 mL of THF was treated with 15 mL of water and 1 drop of concd H_2SO_4 and heated to reflux for 1 h. The solution was cooled and extracted with EtOAc (3×), and the organic layers were washed with saturated $NaHCO_3$ (3×) and brine (1×), dried, filtered, and evaporated to give 0.60 g (68%) of ketone **24**: mp 148.0–149.5 °C; IR (KBr) 1773, 1652; ^{1}H NMR ($CDCl_3$) δ 2.12 (1, ddd, J = 13.6, 11.1, 4.3), 2.62 (1, dd, J = 13.7, 6.5), 2.88 (1, dd, J = 19.3, 8.8), 3.07 (1, dd, J = 19.1, 9.5), 3.66 (1, dd, J = 13.1, 4.3), 3.74 (1, dd, J = 19.9, 11.8), 4.11 (1, d, J = 19.7), 4.25 (1, t, J = 3.9), 4.5 (1, m), 4.54 (2, s), 4.65 (1, t, J = 9.0), 7.3 (5, m); ^{13}C NMR ($CDCl_3$) δ 34.2, 39.2, 51.5, 52.0, 57.4, 58.2, 70.9, 75.1, 127.6, 127.9, 128.5, 137.3, 164.5, 166.8, 205.8; CI MS 315 (MH^+); FAB MS 315; HR FAB calcd for $C_{17}H_{19}N_2O_4$ (MH^+) 315.1345, found 315.1355. Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91. Found: C, 63.67; H, 5.60; N, 8.54.

Registry No. **2a**, 63667-06-1; **2b**, 142800-04-2; **2c**, 142800-05-3; **2f**, 142800-06-4; **2g**, 142800-07-5; **5**, 13504-85-3; **7**, 64187-47-9; **8**, 75776-54-4; **9**, 113490-85-0; **10**, 142800-08-6; **11**, 75776-77-1; **12**, 142800-09-7; **13**, 142800-10-0; **17**, 142800-11-1; **18**, 142800-12-2; **19**, 142865-29-0; **20**, 142800-13-3; **21**, 142800-14-4; **22**, 142800-15-5; **23**, 142865-31-4; **24**, 142865-30-3; BnBr, 100-39-0; 1,2-ethanedithiol, 540-63-6; (*R*)-(+)-1-methoxy-1-(trifluoromethyl)phenylacetyl chloride, 39637-99-5; (*S*)-(−)-1-methoxy-1-(trifluoromethyl)-phenylacetyl chloride, 20445-33-4.

Supplementary Material Available: X-ray data including an ORTEP plot for **20**, experimental procedures and spectral data for **7**, **8**, **9**, **18**, and **19**, ^{1}H NMR spectra for **2b**, **2e**, **2f**, **2g**, **13**, **17**, **18**, **19**, and **24**, and analytical HPLC chromatograms for **18** and **19** (23 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and may be ordered from the ACS; see any current masthead page for ordering information.

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Convenient Method for the Synthesis of C-Alkylated Purine Nucleosides: Palladium-Catalyzed Cross-Coupling Reaction of Halogenopurine Nucleosides with Trialkylaluminums

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Received March 30, 1992

Introduction of various carbon chains onto the ring carbon of the naturally occurring purine nucleosides has been extensively investigated to synthesize biologically active analogs.[1] There have been ample precedents for the preparation method of 2- and 8-alkylpurine nucleosides, and the methods for the direct introduction of alkyl groups are mainly based on the application of radical reaction[2] and C-lithiation.[3] These methods, however, are not always satisfactory with respect to regioselectively, yield, and/or the scope of reactions. Although the cross-coupling of Grignard reagents with aryl halides has achieved great success in the field of synthetic organic chemistry,[4] application of such cross-coupling reactions to 8-bromoadenosine derivatives is far from satisfactory in view of its inefficiency.[5]

On the other hand, the cross-coupling using trialkylaluminums has not been widely investigated.[6] During the course of our studies on the palladium-catalyzed cross-coupling reaction with trialkylaluminums,[7] we have found that trialkylaluminums smoothly coupled with halogenopurine nucleosides. This paper describes a convenient method for the preparation of C-alkylated purine nucleosides.

Cross-coupling of 8-bromoadenosine (**1a**) itself with trimethylaluminum in the presence of palladium catalyst resulted in the recovery of the starting material. When 8-bromoadenosine was protected with a trimethylsilyl group in the coupling reaction, the expected 8-methyladenosine was successfully formed in high yield by the reaction with trimethylaluminum. Thus, treatment of 8-bromoadenosine (**1a**) (1 equiv) with excess hexamethyldisilazane (HMDS) gave quantitatively the corresponding trimethylsilylated 8-bromoadenosine, which was used in the next step without any purification. A mixture

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