teraction between the two ruthenium centers in the imidazolate case. This is valid if the electron mediation is accomplished with the π-bond system of the ligand. Imidazolate ion, however, can possibly make use of its σ-bond system in a manner similar to halides and hydroxide ligands. The relatively fast net rate of electron transfer for $-Ru^{II}-Im-Co^{III}-$ ($k = 6 \pm 1\ s^{-1}$) may be a result of such a mechanism. Note that the rate is faster than the rate of electron transfer in similar binuclear complexes with other bridging N-heterocyclic ligands that have been studied.[17] The σ-bond system of imidazolate anion can interact more effectively with a d-σ acceptor orbital as in cobalt(III) than can many pyridine-type heterocycles. The possible use of the π- as well as the σ-bond system of imidazolate anion renders it a versatile ligand which can interact with σ- and π-donor and -acceptor metal ion orbitals.

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References and Notes

(1) Eichorn, G. L., Ed. "Inorganic Biochemistry", Elsevier: New York, 1973; Vol. II.
(2) The pK_a for the ionization of the pyrrole hydrogen of free imidazole, ImH $\rightleftharpoons Im^- + H^+$, is 14.2–14.5 (see ref 5). In metal complexes of imidazole, the acidity of the pyrrole nitrogen increases resulting in a decrease in the pK_a by as much as five units.
(3) Richardson, J. S.; Thomes, K. A.; Rubin, B. H.; Richardson, D. C. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 1349.
(4) Palmer, G.; Babcock, G. T.; Vickery, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 2206.
(5) For a comprehensive review of imidazole complexes, see Sundberg, R. J.; Martin, R. B. *Chem. Rev.* **1974**, *74*, 471.
(6) (a) Nappa, M; Valentine, J. S.; Synder, P. A. *J. Am. Chem. Soc.* **1977**, *99*, 5799–5800. (b) Evans, C. A.; Rubenstein, D. L.; Geier, G.; Erni, I. W. *ibid.* **1977**, *99*, 8106–8108.
(7) (a) Kolks, G.; Lippard. S. J. *J. Am. Chem. Soc.* **1977**, *99*, 5804. (b) Kolks, G.; Frihart, C. R.; Rabinowitz, H. N.; Lippard, S. J. *ibid.* **1976**, *98*, 5720.
(8) Isied, S.; Taube, H. *Inorg. Chem.* **1974**, *13*, 154.
(9) Harrowfield, J. M.; Norris, V.; Sargeson, A. M. *J. Am. Chem. Soc.* **1976**, *98*, 7782.
(10) (a) Sundberg, R. J.; Shepherd, R. E.; Taube, H. *J. Am. Chem. Soc.* **1972**, *94*, 6558. (b) Sundberg, R. J.; Bryan, R. F.; Taylor, Jr., I. F.; Taube, H. *Ibid.* **1974**, *96*, 381.
(11) Isied, S.; Taube, H. *Inorg. Chem.* **1976**, *15*, 3070.
(12) Isied, S.; Taube, H. *J. Am. Chem. Soc.*, **1973**, *95*, 8198.
(13) Calcd for $[Ru_2C_3H_{27}N_{10}S_2O_8](BF_4)\cdot 2H_2O$ (**1a**): C, 5.00; H, 4.34; N, 19.44. Found: C, 4.84; H, 4.94; N, 18.43. Calcd for $[Ru_2C_3H_{30}N_{11}SO_4](BF_4)_3$ (**1b**): C, 4.65; H, 3.88; N, 19.78. Found: C, 4.80; H, 3.84; N, 17.95. Calcd for $[CoRuC_3H_{30}N_9SO_4](BF_4)_3$ (**1c**): C, 4.89; H, 4.10; N, 20.91; Co, 8.00; Ru, 13.72. Found, C, 5.40; H, 4.43; N, 20.18; Co, 7.6; Ru, 13.0. We have no reasonable explanation for the low nitrogen content in the above compounds.
(14) The residence times of all the ligands in the metal coordination spheres of the complexes in question are much longer than the electron-transfer time scale. The only exception to this is $Ru^{II}SO_4$ where the rate of loss of sulfate for a closely related system has been determined ($t_{1/2} = 0.3$ s).[12] This fact presents slight complications as to which species, the $Ru^{II}SO_4$ or the $Ru^{II}OH_2$, one is dealing with.
(15) $k = 1 \times 10^{13} (\exp(-\Delta G^{\ddagger}/RT)\ s^{-1}$, where 10^{13} is a frequency factor; $\Delta G^{\ddagger}$ is calculated from $\lambda_{max}/4$ in the appropriate units. Hush, N. *Prog. Inorg. Chem.* **1967**, *8*, 391.
(16) $[(NH_3)_5Ru-Im-Ru(NH_3)_4(SO_4)](BF_4)_3$, 0.7×10^{-3} M, and $[(NH_3)_5Ru(ImH)]^{3+}$, 1.4×10^{-3} M in D_2O, 22 °C.
(17) Fischer, H.; Tom, G. M.; Taube, H. *J. Am. Chem. Soc.* **1976**, *98*, 5512.
(18) The rate of intramolecular electron transfer was monitored at λ 440, 450, and 470 nm using an Aminco stopped-flow spectrophotometer. The species $-Ru^{II}-Im-Co^{III}-$ was generated at concentration of 5.0×10^{-3} to 1.0×10^{-3} M with varying concentrations of Eu^{2+}.
(19) The corresponding intermolecular processes at similar concentrations take place on a time scale of minutes.
(20) Kitson, R. E. *Anal. Chem.* **1950**, *22*, 664.
(21) This conclusion is based on the UV spectrum of the product of the electron-transfer reaction. A λ_{max} at 312 nm corresponds to $[(SO_4)(NH_3)_4Ru(ImH)]^+$ (Table I).
(22) Creutz, C.; Taube, H. *J. Am. Chem. Soc.*, **1973**, *95*, 1088.
(23) Taube, H. *Adv. Chem. Ser.* **1977**, *No. 162*, 127–144.
(24) Note that the rate of loss of sulfate is not known for the mixed valence species and therefore the ligand trans to imidazolate can be SO_4^{2-}, OH_2, or OH^-. We are currently attempting the synthesis of the symmetrical decaammine-imidazolate complexes for a detailed study of the solvent dependence of the intervalence band for $Ru^{II}-Im-Ru^{III}$ and the magnetic exchange properties of the fully oxidized $Ru^{III}-Im-Ru^{III}$ complex.
(25) Bandwidth = 8.0 *kK*; calcd bandwidth = 4.1 *kK* using the equations given in ref 15.
(26) (a) Landrum, J. T.; Reed, C. A.; Hatano, K.; Scheidt, W. R. *J. Am. Chem. Soc.*, **1978**, *100*, 3232–3234. (b) Beattie, J. K.; Hush, N. S.; Taylor, P. R.; Raston, C. L.; White, A. H. *J. Chem. Soc. Dalton Trans.*, **1977**, *11*, 1121–1124.

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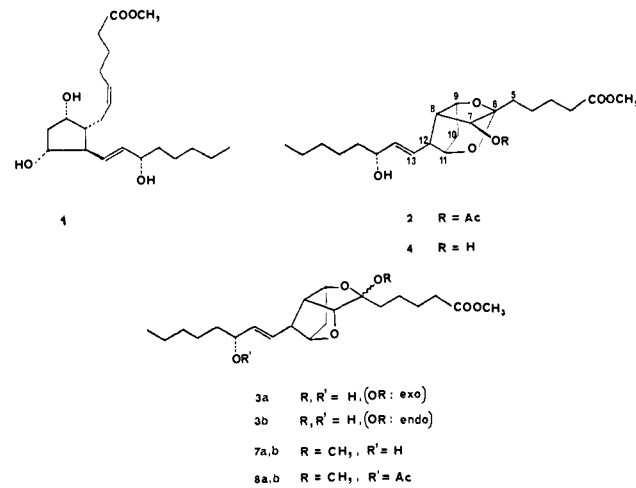
A Novel Functionalization of Prostaglandin Skeleton. Addition of Thallium Triacetate to $PGF_{2\alpha}$ Methyl Ester

Sir:

According to synthetic strategies published to this date, the preparation of the highly potent antiaggregatory PGI_2 and analogues starts with the electrophilic activation of the 5,6 double bond of $PGF_{2\alpha}$ (or equivalents) accompanied by the formation of the five-membered ring through participation of the 9-positioned OH (or SH) function. The cyclization was shown to proceed with various electrophilic agents, viz., I^+, Br^+, $PhSe^+$, and Hg^{2+}.[1] The well-known electrophilic properties of Tl^{3+} and the ease with which C-Tl bonds are broken[2] have prompted us to test the applicability of Tl^{3+} as an electrophilic agent in these processes. We have found that the reaction of $PGF_{2\alpha}$ methyl ester (**1**) with thallium triacetate



proceeds with the participation of both C-9 and C-11 hydroxyl functions and leads to the formation of two novel dioxatricyclo systems, **2** and **3**, hiterto unknown in prostaglandin chemistry. These products may be readily converted into other derivatives with the prostaglandin skeleton functionalized in position 7.

Treatment of **1** with 3 molar equiv of thallium triacetate in acetic acid (90 mL/g of **1**) at 25 °C for 24 h produced a 1:2.5 mixture of **2** and **3**. Chromatographic separation gave the pure substances (R_f 0.54 for **2** and R_f 0.28 for **3**, 2:1 ethyl acetate–hexane) as oils in 70–75% yields (overall from **1**). Spectral data disclosed that the highly acid-sensitive **2** is isomerically pure, while the more polar product is a chromatographically nonseparable mixture of two isomers, **3a** and **3b** (~1:3).

The structure and stereochemistry of these novel systems as shown were unambiguously proved by means of the IR and mass spectral[2,3,4] data and careful analysis of the ^1H and ^{13}C spectra,[5,6] aided by the evaluation of characteristics chemical-shift changes upon derivatization of **2** and **3a,b**. Chemical transformations provided corroboration for the correctness of

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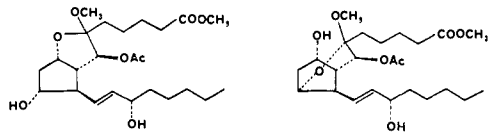
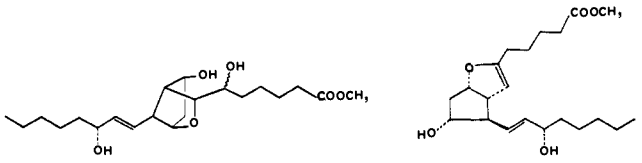
structures **2** and **3a,b.** Thus treatment of **2** in methanol with potassium carbonate at 25 °C for 2 h afforded the diol **4.**[7] The presence of an internal ketal moiety was evidenced by transketalization. Reaction of **2** with methanol in the presence of boron trifluoride etherate at 25 °C for 1 h gave **5**[8,9] and **6.**[8]



5 6

Similar methanolysis of **3a,b** at 25 °C for 15 min furnished the isomeric methyl ketals **7a,b**[8] which, using acetic anhydride-pyridine at 25 °C for 30 min, were converted to **8a,b.**[8] The masked oxo function of **3a,b** could be reduced by sodium bobohydride in ethanol, yielding the readily separable isomeric triols **9a** and **9b.**[8]



9a,9b 10

Formation of **2** and **3a,b** upon the action of thallium triacetate may be interpreted by assuming **10** as the intermediate, produced via formation of the 6,9α-oxido ring and a carbenium ion at C-5 after the heterolysis of the primary C–Tl bond, which is followed by hydride shift and the loss of a proton from C-6 or C-7. Occurrence of the highly unstable **10** in the enzymatic conversion of arachidonic acid by rat stomach homogenates has been reported recently by Sih et al.[10] The reaction of an additional mole of thallium triacetate[11] with the endo double bond, aided by the OH group at C-11 and the solvent molecules as nucleophiles, produces **2**[12] and **3a,b** simultaneously. This mechanism readily explains the stereochemistry at C-6 and C-7 in **2** and **3a,b.**

We believe that the underlying reactions may have implications also outside the prostaglandin field.

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References and Notes

(1) (a) Corey, E. J.; Keck, G. E.; Székely, I. *J. Am. Chem. Soc.* **1977,** *99,* 2006–2008. (b) Johnson, R. A.; Lincoln, F. H.; Thompson, J. L.; Nidy, E. G.; Mizsak, S. A.; Axen, U. *ibid.* **1977,** *99,* 4182–4184. (c) Fried, J.; Barton, J. *Proc. Natl. Acad. Sci. U.S.A.* **1977,** *74,* 2199–2203. (d) Tömösközi, I.; Galambos, G.; Simonidesz, V.; Kovács, G. *Tetrahedron Lett.* **1977,** 2627–2628. (e) Whittaker, N. *Ibid.,* **1977,** 2805–2808. (f) Corey, E. J.; Székely, I.; Shiner, C. S. *ibid.* **1977,** 3529–3532. (g) Nicolau, K. C.; Barnette, W. E.; Gasic, G. P.; Magolda, R. L.; Sipio, W. J. *J. Chem. Soc., Chem. Commun.* **1977,** 630–631.

(2) McKillop, A.; Taylor, E. C. *Adv. Organomet. Chem.* **1973,** *11,* 147–161.

(3) Mass spectra were taken on Varian MAT SM-1 instrument.

(4) (a) Mass spectrum of **2** showed $M^{+}\cdot$ at 424.2419 (calcd for $C_{23}H_{36}O_7$, 424.2461) and the characteristic fragment ions at *m/e* 364, 346, 174, 143 (base peak), and 99. (b) Mass spectrum of **3a,b** showed $M^{+}\cdot$ at 382.2344 (calcd for $C_{21}H_{34}O_6$, 382.2355) and prominent fragment ions at *m/e* 222.1598 (M − $HOOC(CH_2)_4COOCH_3$) (calcd for $C_{14}H_{22}O_2$, 222.1620), 204, 161, 143, and 99 (base peak). Ions *m/e* 161 (formed via H rearrangement) and 143 (from 161 − H_2O and from 6-keto form $M^{+}\cdot$) indicate the presence of C-6 lactol. Ion *m/e* represents the C-7–C-20 moiety of **3;** the high abundance of ions formed in this fragmentation pathway is assumed to be due to the 7,11α-oxido group.

(5) ^1H and ^{13}C NMR spectra were recorded on a Varian XL-100 FT spectrometer operating at 100.1 and 25.16 MHz, respectively.

(6) Selected ^1H and ^{13}C NMR chemical shifts follow (* indicates exo C-6 OH). ^1H NMR (δ, $CDCl_3$): **2,** 2.86 (m, 1 H, C-8 H), 3.00 (m, 1 H, C-12 H), 4.05 (m, 1 H, C-15 H), 4.32 (m, 1 H, $J_{10,11}$ = 1.5 + 1.5 Hz, $J_{9,11}$ = 2 Hz, C-11 H), 4.77 (m, 1 H, C-9 H), 4.96 (d, 1 H, $J_{7,8}$ = 0.5 Hz, C-7 H), 5.38 (dd, 1 H, C-13 H), 5.52 (dd, 1 H, C-14 H), 3.66 (s, 3 H, $-COOCH_3$), 2.06 (s, 3 H, $7-OCOCH_3$); **3a,b,** 2.89 + 3.10* (m, 1 H, C-8 H), 2.95 (m, 1 H, C-12 H), 3.9 (m, 1 H, C-15 H), 4.15 + 4.08* (m, 1 H, $J_{10,11}$ = 1.5 + 1.5 Hz, $J_{9,11}$ = 1 Hz, C-11 H), 4.48 + 4.52* (m, 1 H, C-9 H), 3.92 + 3.95* (dd, 1 H, $J_{7,8}$ = 3 Hz, $J_{7,9}$ = 1 Hz, C-7 H), 5.42 (dd, 1 H, C-13 H), 5.55 (dd, 1 H, C-14 H), 3.56 (s, 3 H, $-COOCH_3$). ^{13}C NMR (δ, $CDCl_3$): **2,** 30.94 (C-5), 107.66 (C-6), 81.39 (C-7), 47.56 (C-8), 80.79 (C-9), 36.42 (C-10), 78.36 (C-11), 52.96 (C-12), 128.65 (C-13), 135.28 (C-14), 72.43 (C-15), 21.16 + 170.27 ($-O-CO-CH_3$); **3a,b,** 37.81 + 36.46* (C-5), 106.0 + 107.0* (C-6), 82.62 + 83.87* (C-7), 51.02 + 49.56* (C-8), 77.75 + 78.47* (C-9), 39.16 + 39.77* (C-10), 78.90 + 79.08* (C-11), 52.72 + 51.92* (C-12), 125.15 + 126.14* (C-13), 137.03 + 136.66* (C-14), 72.32 (C-15).

(7) Relevant ^{13}C NMR acetylation shifts (Δ_{2-4}: −1.35 (C-6), + 1.02 (C-7), and −2.21 (C-8).

(8) ^1H and ^{13}C spectral data of all derivatives were consistent with their structures.

(9) The formation and cleavage of the intramolecular oxygen bridges as in **2** and **3** involving C-11 OH are accompanied by characteristic changes of the C-11 H coupling constants; substantially smaller values are observed for **2** and **3** than for **1** and **5.**

(10) Sih, C. J.; Huang, Fu-Chih. *J. Am. Chem. Soc.* **1978,** *100,* 643–645.

(11) With 1 mol of thallium triacetate, besides unchanged **1,** only small amounts of **2** and **3** could be detected.

(12) After completion of this manuscript, we learned about the paper by Shimoji, K., et al. *J. Am. Chem. Soc.* **1978,** *100,* 2547–2548, describing the synthesis of **10** and a derivative of **2.**

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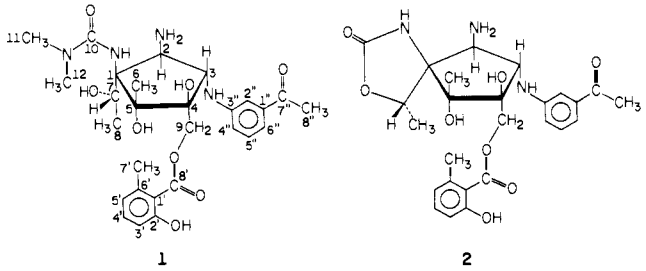
Biosynthesis of the Antitumor Antibiotic Pactamycin. A Methionine-Derived Ethyl Group and a C_7N Unit[1]

Sir:

Pactamycin (**1**), an antibiotic isolated from *Streptomyces pactum* var. *pactum,*[2a] is one of the more potent cytotoxic agents in vitro, inhibiting KB cells at 0.003 μg/mL (ID_{50}), and it has in vivo activity against a number of mammalian tumors.[2b] It is also active against gram-positive bacteria (MIC 0.8



1 2

μg/mL vs. *B. subtilis*), though its toxicity[2b] prevents any clinical applications, and it has proved valuable as a biochemical tool in studies of protein synthesis.[3] In addition to its bioactivity the uniquely branched, multiply hydroxylated and aminated, cyclopentane ring[4] is of considerable interest for its obscure biosynthetic origin. We report here that pactamycin is derived from a mixed biosynthetic pathway involving glucose, acetate, and methionine.

Administration of labeled precursors to a culture of *S. pactum* (Table I) showed that L-[*methyl*-^{14}C]methionine was incorporated into pactamycin to the extent of 0.020%, while [*carboxy*-^{14}C]acetate and D-[1-^{14}C]glucose were incorporated into pactamyçate (**2**), which is coproduced in this medium, to the extent of 0.093 and 0.061%, respectively. Conversion of pactamycin labeled by [*methyl*-^{14}C]methionine to pactamyçate indicated loss of 40% of the label; thus, the *N*-methyl groups are derived from methionine.

Administration of ^{13}C-labeled precursors was followed by

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