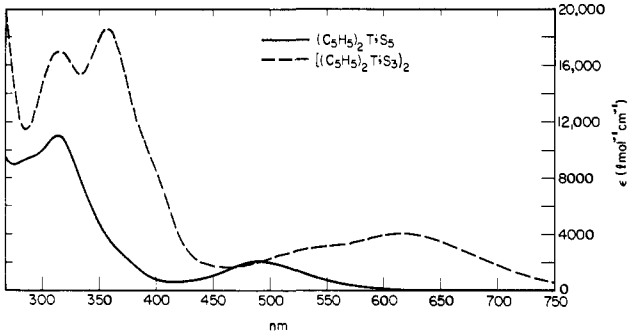
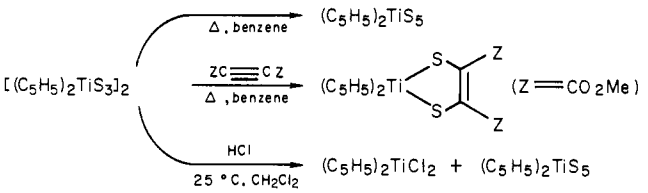


Figure 3. Electronic absorption spectrum of $(C_5H_5)_4Ti_2S_6$ and $(C_5H_5)_2TiS_5$ in CH_2Cl_2.

Scheme I



for all nonhydrogen atoms gave $R = 0.036$ and $R_w = 0.043$.[13]

The structure of **2** (Figure 1) consists of an eight-membered ring of approximate D_2 symmetry and contains alternating $(\eta^5\text{-}C_5H_4CH_3)_2Ti$ and S_3 fragments. Unlike cyclo-S_8,[14] **2** adopts a cradle conformation (Figure 2) wherein the titanium atoms are positioned at sites adjacent to the apical sulfurs. There is some asymmetry in the way that each S_3 unit interacts with a given titanium atom as manifested not only in the TiS distances but also in the Ti–S–S–S and STiSS dihedral angles (62.8° (average) vs. 66.8° (average) and 69.0° (average) vs. 58.9° (average), respectively). The coordination sphere about the titanium atoms resembles that observed for Cp_2TiS_5.[15,16] The XMX angle of Cp_2MX_2 complexes is known to be sensitive to the occupancy of the metal-based a_{1g} orbital;[16] the observed STiS angle is inconsistent with the titanium(III) formulation (suggested by its blue color) where an angle of ca. 89° would be expected (cf. $(C_5H_5)_2VS_5$).[15] While the S–S bond distances are completely normal for single bonds, the S–S–S angles are expanded and the dihedral angles are compressed relative to known cyclic polysulfides.[14]

One unique feature associated with **2** is its blue color which results from a low-energy absorption band centered at 610 nm (Figure 3). Such an absorption maximum is unusual for bis(cyclopentadienyl)titanium(IV) complexes but is reminiscent of that for S_8^{2+} (λ_{max} = 590 nm, ϵ = 2500 L mol^{-1} cm^{-1}).[17,1] The proposed titanium(IV) oxidation state requires the S_3^{2-} formulation while the long transannular S···S bond distances.[19] militate against strong S···S interactions of the type recognized for S_8^{2+},[20] S_4N_4, and other electron-deficient sulfur rings.[21,22]

We have surveyed the reactivity of **2** and some of the salient results are indicated in Scheme I. Heating **2** in benzene solution promotes the formation of the red pentasulfide, **1**, together with some insoluble, presumably polymeric residue. **2** shows enhanced reactivity relative to **1** toward dimethylacetylenedicarboxylate, affording the dithiolene.[23] Surprisingly, protonolysis of **2** with anhydrous HCl does not lead to scission of all titanium sulfur bonds but instead affords an apparently equimolar mixture of $(C_5H_5)_2TiCl_2$ and **1**. A likely mechanism for this process involves the formation of an intermediate containing an η^1-S_3H moiety followed by cyclization with concomitant elimination of $(C_5H_5)_2Ti(SH)Cl$.

Acknowledgment. This research was supported by the National Science Foundation and in part by the National Institutes of Health through a Biomedical Research Grant. Field desorption mass spectra were obtained in part under a grant from the National Cancer Institute (No. CA 11, 388).

(13) The function minimized was $\sum w||F_o| - |F_c||^2$, $R = \sum||F_o| - |F_c||/\sum|F_o|$, and $R_w = [\sum w||F_o| - |F_c||^2/\sum w|F_o|^2]^{1/2}$.
(14) Meyer, B. *Chem. Rev.* **1976**, *76*, 367–388 and references therein.
(15) Epstein, E. F.; Bernal, I. *J. Organomet. Chem.* **1971**, *26*, 229–245.
(16) Muller, K. G.; Petersen, J. L.; Dahl, L. F. *J. Organomet. Chem.* **1976**, *111*, 91–112.
(17) Gillespie, R. J.; Passmore, J.; Ummet, P. K.; Vaidya, O. C. *Inorg. Chem.* **1971**, *10*, 1327–1332.
(18) S_3^- exhibits a λ_{max} at 620 nm (ϵ = 4500 L mol^{-1} cm^{-1}): Chivers, T. "Homoatomic rings Chains, and Macromolecules of Main Group Elements"; Reingold, A. L. Ed.; Elsevier: New York, 1977; pp 499–537.
(19) S(1)···S(3) = 3.349 (1) Å; S(1)···S(4) = 3.606 (1) Å; S(1)···S(6) = 3.529 (1)Å.
(20) Davies, C. G.; Gillespie, R. J.; Park, J. J.; Passmore, J. *Inorg. Chem.* **1971**, *10*, 2781–2784.
(21) Musker, W. K. *Acc. Chem. Res.* **1980**, *13* 200–206.
(22) For a general review, see ref 18.
(23) The conversion of $(C_5H_5)_2TiS_5$ to the dithiolene by reaction with dimethylacetylenedicarboxylate requires more vigourous conditions than those for $(C_5H_5)_5Ti_2S_6$: Bolinger, C. M; Rauchfuss, T. B., to be published. This dithiolene has been subsequently characterized crystallographically.
(24) Subsequent to submission of this article we have prepared and characterized the *red* complex, $(CH_3C_5H_4)_4Ti_2S_4$: Bolinger, C. M., Rauchfuss, T. B. to be submitted for publication.

Synthesis of the Left-Hand Segment of the Antitumor Agent CC-1065

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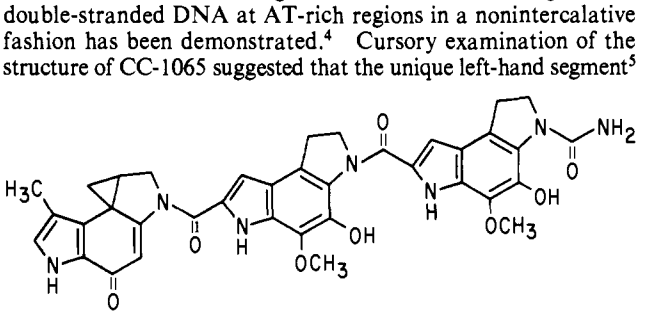
Received June 1, 1981

Recently a highly cytotoxic agent, CC-1065, was isolated from *Streptomyces zelensis*[1] and shown to have novel structure **1**.[2] This substance exhibited notable potency against L1210 in vitro and against the L1210 and P388 leukemias in mice as well as B16 melanoma,[3] proving to be the most cytotoxic antitumor agent known. Preferential binding of CC-1065 in the minor groove of double-stranded DNA at AT-rich regions in a nonintercalative fashion has been demonstrated.[4] Cursory examination of the structure of CC-1065 suggested that the unique left-hand segment[5]



1

incorporates a potential "alkylating" capability to the structure. This capability might be a partial mechanism of action. To isolate

(1) Hanka, L. J., Dietz, A., Gerpheide, S. A., Kuentzel, S. L., Martin, D. G. *J. Antibiot.* **1978**, *31*, 1211–1217.
(2) Martin, D. G.; Chidester, C. G.; Duchamp, D. J.; Mizsak, S. A. *J. Antibiot.* **1980**, *33*, 902–903. See also: Chidester, C. G.; Krueger, W. C.; Mizsak, S. A.; Duchamp, D. J.; Martin, D. G. *J. Am. Chem. Soc.*, submitted for publication.
(3) Martin, D. G.; Hanka, L. J.; Neil, G. L. *Proc. Am. Assoc. Cancer Res.* **1978**, *19*, 99.
(4) Swenson, D. H.; Krueger, W. C.; Lin, A. H.; Schpok, S. L.; Li, L. H. Proceedings of the American Association of Cancer Research, Washington, DC, April 1981; Abstr. 2336.
(5) The identical middle and right-hand segments, 1,2-dihydro-3*H*-pyrrol[3,2-*c*]indoles, are the same as the 3′,5′-AMP phosphodiesterase inhibitor, PDE-I, isolated by: Enomoto, Y.; Furutani, Y.; Naganawa, H.; Hamada, M.; Takeuchi, T.; Umezawa, H. *Agric. Biol. Chem.* **1978**, *42*, 1331–1336. A 12-step synthesis of this ring system was reported by the same group: Komoto, N.; Enomoto, Y.; Miyagaki, N.; Tanaka, Y.; Nitanai, K.; Umezawa, H. *Ibid.* **1979**, *43*, 557–559.

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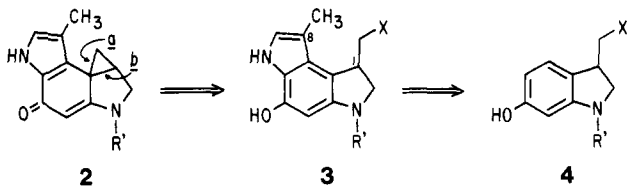
Scheme I



2 3 4

the biological activity of this segment we undertook a synthesis of this cyclopropylpyrroloindole (**2**).

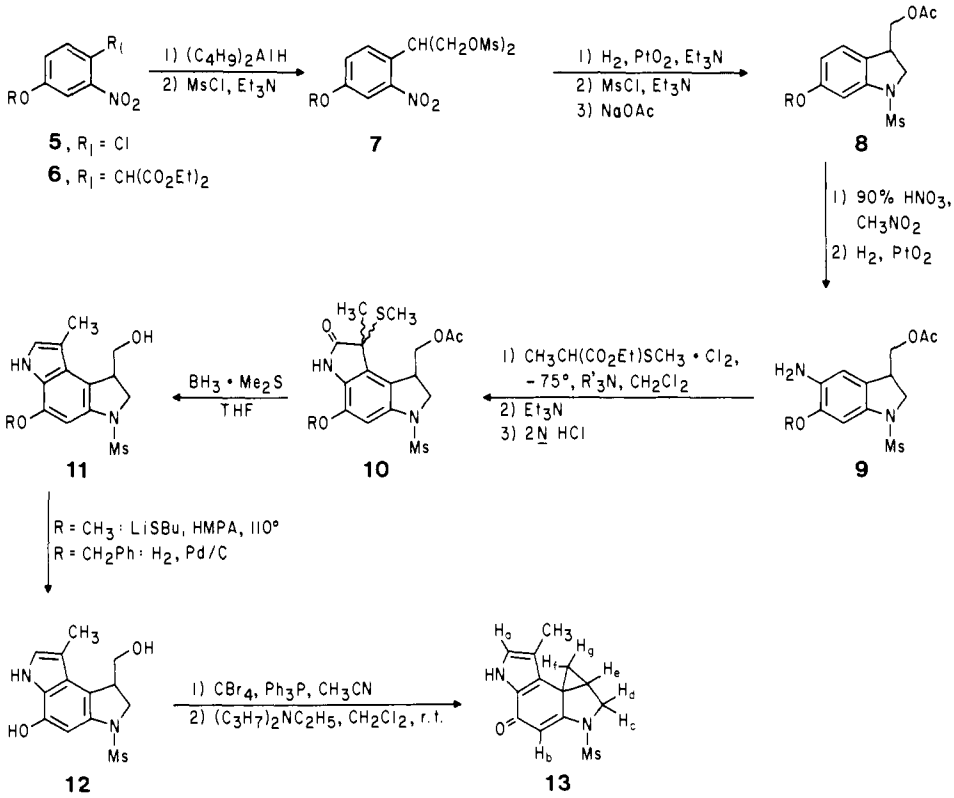
Several critical features in the strategy for synthesis of **2** (Scheme I) included (1) the formation bond a to secure the cyclopropylspirocyclohexadienone **2** from the penultimate intermediate **3** through an intramolecular para alkylation,[6] (2) the aromatic substitution pattern of **4** to regiospecifically direct introduction of the 8-methylindolic group of **3**, and (3) an efficient, regiospecific synthesis of 6-hydroxyindolines **4**.

Commercially available 4-chloro-3-nitroanisole was converted via the method of Bourdais[7] [$NaCH(CO_2Et)_2$, DMF, Δ] to aryl malonate **6** (Scheme II) in 70% yield, introducing regiospecifically the requisite 3-carbon homologation in one step. The subsequent strategy for preparing indoline **4** required conversion of malonate **6** to a diol. Although reductions of enolizable 1,3-dicarbonyl compounds are often accompanied by elimination[8] we found that diisobutylaluminum hydride at 0–25 °C in THF/toluene reproducibly afforded the 2-aryl-1,3-propanediol[9] in 50–60% yields.

The bismesylate **7**[9] (CH_3SO_2Cl, CH_2Cl_2, Et_3N; mp 122–123 °C, R = CH_3) was converted to indoline **8** by a reductive cyclization[10] employing catalytic hydrogenation (0.05 M in ethanol) in the presence of 1 equiv of triethylamine. The relatively labile indoline thus formed was stabilized by conversion to the methylsulfonamide[11] (0 °C, CH_2Cl_2; mp 122–123 °C, R = CH_3), and the 3-methylene mesylate was exchanged for an acetate (10 equiv of NaOAc, EtOH, DMF, Δ) to give **8**[9] in 70% yield from **7**. [NMR ($CDCl_3$) δ 7.17 (d, 1 H, J = 8.5 Hz), 7.02 (dd, 1 H, J = 2 Hz), 6.60 (dd, 1 H, J = 2, 8.5 Hz), 4.18 (d, 2 H, J = 6 Hz), 4.1–3.4 (m, 3 H), 3.78 (s, 3 H), 2.91 (s, 3 H), 2.05 (s, 3 H)].

As anticipated, the substitution pattern of **8** directed nitration exclusively to the 5 position as determined by disappearance of the 5-H (dd, 6.60 Hz) in the ^1H NMR (mp 175–177 °C, R = CH_3). Catalytic reduction gave **9**[9] in 80% yield. A modification of the oxindole synthesis of Gassman et al.[14,15] was employed to secure **3**. Addition of **9** and 1 equiv of a hindered base [1,8-bis(dimethylamino)naphthylene[17] or isopentyldiisopropylamine] to the chlorine complex of ethyl α-(mercaptomethyl)propionate[18] (2 h, −75 °C) followed by a triethylamine catalyzed Sommelet–Hauser rearrangement and an acid-induced cyclization gave **10**[9]

Scheme II



5, R_1 = Cl
6, R_1 = $CH(CO_2Et)_2$
7 **8** **9** **10** **11** **12** **13**

(6) Baird, R.; Winstein, S. *J. Am. Chem. Soc.* **1963**, *85*, 567–578. They described the first example of this chemistry to prepare the unstable spiro-[2.5]octa-1,4-dienone.

(7) Bourdais, J.; Mahieu, C. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1966**, *263*, 84–87.

(8) Marshall, J. A.; Anderson, N. H.; Hochstetler, A. R. *J. Org. Chem.* **1967**, *32*, 113–119.

(9) All new compounds exhibited acceptable IR, NMR, elemental analyses, and high-resolution mass spectra. Yields refer to isolated materials.

(10) Hengartner, U.; Batcho, A. D.; Blount, J. F.; Leimgruber, W.; Larscheid, M. E.; Scott, J. W. *J. Org. Chem.* **1979**, *44*, 3748–3752. They report a method to produce indoles via an in situ reduction–cyclization. We are unaware of a reductive cyclization (i.e., **7** → **8**) to produce indolines.

(11) We have also successfully employed $(CF_3SO_2)_2O$ and $(CH_3)_3SiCH_2CH_2OCOCl$ as N_1-protecting groups to form the corresponding trifanilide and β-(trimethylsilyl)ethoxy carbamate. Although these latter two groups can be conveniently removed by LAH/Et_2O[12] and CsF (or Bu_4NF),[13] respectively, they allow poorer yields later in the synthesis (e.g., **9** → **10**).

(12) Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, 3839–3842.

(13) Carpino, L. A.; Tsao, J.-H.; Ringsdorf, H.; Fell, E.; Hettrich, G. *J. Chem. Soc., Chem. Commun.* **1978**, 358–359.

(14) Gassman, P. G.; Gruetzmacher, G.; van Bergen, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 5512–5517.

(15) The "direct" method of synthesis of indoles reported by Gassman and co-workers[16] was unacceptable in preparing **11** (~2% yield). A model study employing *o*-anisidine and $CH_3(SCH_3)CHCHO{\cdot}Cl_2$ resulted in only a 20% yield of 7-methoxy-3-methylindole.

(16) Gassman, P. G.; van Bergen, T. J.; Gilbert, D. P.; Cue, B. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 5495–5508.

(17) Alder, R. W.; Goode, N. C.; Miller, N.; Hibbert, F.; Hunte, K. P. P.; Robbins, H. J. *J. Chem. Soc., Chem. Commun.* **1978**, 89–90.

(18) Bülmann, E.; Jensen, K. A. *Bull. Soc. Chim. Fr.* **1936**, 2310–2320.

as a mixture of diastereoisomers in 25% yield (80% based on **9** recovered in the acid fraction).

Attempts to convert the 3-methyl-3-(alkylthio)oxindole **10** to **11** with lithium aluminum hydride[14,19] proved unsuccessful. Indeed, the procedure was sluggish or completely ineffective in several model studies. Borane reduction of 3-substituted oxindoles has been reported to afford indolines.[20] However, with the additional 3-alkylthio substituent, we observed essentially quantitative conversion to the *3-substituted indoles* on several model oxindoles with $BH_3{\cdot}SMe_2$. Treatment of **10** with an excess of $BH_3{\cdot}SMe_2$ at room temperature for 24 h likewise afforded **11** in 95% yield. Normally, the entire procedure **9** → **11** was accomplished without isolation of intermediates in a 2-pot, 24-h process.

Our initial efforts in the synthesis of **13** involved the methyl ether as the phenol protecting group (e.g., **5**, R = CH_3). After numerous failures with acidic-type reagents[21] to deprotect **11** to **12**, we found that mercaptide anions[22] accomplished this transformation in 40–60% yields. However, the yields decreased on scaleup. Therefore, the synthesis was repeated with benzyl ether (**5**, R = CH_2Ph),[23] which was readily removed to give **12**[9] [90%; NMR (acetone-d_6) δ 7.8 (br s, 1 H), 7.03 (s, 1 H), 6.83 (s, 1 H), 4.25–3.25 (m, 5 H), 2.86 (s, 3 H), 2.36 (s, 3 H)]. The methylsulfonyl group on anilines can be cleaved with sodium (2-methoxyethoxy)aluminum hydride.[24] This procedure was successful with **6** and should allow for the introduction of other groups on the indoline nitrogen at this, or later, juncture.

The concept of forming bond a as an entry to the cyclopropylspirocyclohexadiene moiety was validated by first converting the alcohol to the bromide[25] followed by exposure to a tertiary amine to give **13**. This can be accomplished in one pot in 70% yield. The structure of **13** was based on ^1H NMR, IR, UV, MS,[26] and single-crystal X-ray analysis.[29]

(19) Wieland, T.; Grimm, D. *Chem. Ber.* **1965**, *98*, 1727.

(20) McEvoy, F. J.; Allen, G. R., Jr. *J. Org. Chem.* **1973**, *38*, 3350–3352. Borane dimethyl sulfide is preferred for the reduction of 3,3-dimethyloxindole to 3,3-dimethylindoline (Hester, J. B., unpublished results, The Upjohn Company).

(21) For example: McOmie, J. F. W.; Watts, M. L.; West, D. E. *Tetrahedron* **1968**, *24*, 2289–2292. Vickery, E. H.; Pahler, L. F.; Eisenbraun, E. J. *J. Org. Chem.* **1979**, *44*, 4444–4446. Hanessian, S.; Guindon, Y. *Tetrahedron Lett.* **1980**, 2305–2308. Williard, P. G.; Fryhle, C. B. *Ibid.* **1980**, 3731–3734. This procedure afforded some of the desired **12**.

(22) Kelly, T. R.; Dali, H. M.; Tsang, W.-G. *Tetrahedron Lett.* **1977**, 3859–3860 and ref 2–4 described therein.

(23) Prepared in 95% yield from 4-chloro-3-nitroanisole: 48% HBr/AcOH, 120 °C, 24 h; $PhCH_2Br$, K_2CO_3, acetone, DMF; mp 46.5–48.7 °C.

(24) Gold, E. H.; Babad, E. *J. Org. Chem.* **1972**, *37*, 2208–2210.

(25) The bromide derivative of **12** was isolated by rapid preparative TLC and structure determined by ^1H NMR and MS (positive Beilstein). On prolonged contact with silica gel it is converted to **13**.

(26) ^1H NMR ($CDCl_3$, 200 MHz) δ 9.5 (br s, 1 H), 6.83 (dd, H_a), 6.34 (s, H_b), 4.10 (d, H_c), 3.93 (dd, H_d), 3.04 (s, 3 H), 2.93 (m, H_e), 2.00 (d, 3 H), 1.97 (dd, H_f), 1.37 (dd, H_g); $J_{c,c} = 0.0$, $J_{c,d} = 9.7$, $J_{d,e} = 4.7$, $J_{e,f} = 7.7$, $J_{g,g} = 4.4$, $J_{f,g} = 4.4$, $J_{NH,a} = 2.0$, $J_{a,CH_3} \leq 1.0$ Hz is consistent with ^1H NMR of CC-1065[2] and 3-azabicyclo[3.1.0]hexane.[27] IR ($CHCl_3$)[28] 3450, 3400–3100 (NH, OH), 1620 (CO), 1360, 1160 cm^{-1} (SO_2). UV (MeOH)[2] λ 224 (ε 3 × 10^4), 272 (4.8 × 10^4) 338 (3 × 10^4). MS, *m/e* calcd for $C_{13}N_{14}N_2O_3S$: 278.0725. Found: 278.0725.

(27) Wendisch, D.; Naegele, W. *Org. Magn. Reson.* **1970**, *2*, 619–624.

(28) Marx, J. N.; Argyle, J. C.; Norman, L. R. *J. Am. Chem. Soc.* **1974**, *96*, 2121. See also: Gramlich, W.; Plieninger, H. *Helv. Chim. Acta* **1979**, *112*, 1573–1582.

(29) *R* = 0.079 on 2322 reflections: Chidester, C. G., unpublished results, Upjohn Co., 1981. Full details will be disclosed later.

Additions and Corrections

Photochemistry of Cis-Fused Bicyclo[4.*n*.0]-2,4-dienes. Ground State Conformational Control [*J. Am. Chem. Soc.* **1980**, *102*, 4456]. WILLIAM G. DAUBEN* and MICHAEL S. KELLOGG, Department of Chemistry, University of California, Berkeley, California 94720.

On page 4459, the last paragraph in the left column should read as follows: The minor primary product, *anti,cis*-tricyclo-[5.4.0.$0^{8,11}$]undec-9-ene (**27**), the product predicted by orbital symmetry consideration (disrotatory), was formed in 3% yield upon extended irradiation. The structure was determined by spectral analysis and by its stereospecific conversion to the cis diene **3** at 220 °C. Assignment of the anti stereochemistry was based on the very small NMR coupling of the bridgehead allylic protons.

Crystal and Molecular Structure of Cofacial Dicopper Hexyldiporphyrin-7 [*J. Am. Chem. Soc.* **1980**, *102*, 7115]. MARCOS H. HATADA, A. TULINSKY,* and C. K. CHANG, Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

Page 7116: the intra- and intermolecular slip angles are interchanged—intra should be 46.4°, inter should be 43.5°.

Pauling "3-Electron Bonds", "Increased-Valence", and 6-Electron 4-Center Bonding [*J. Am. Chem. Soc.* **1980**, *102*, 5195]. RICHARD D. HARCOURT, Department of Physical Chemistry, University of Melbourne, Parkville, Victoria 3052, Australia.

Page 5196 above eq 3 and page 5197 two lines above references: replace "obtained" with "obtain".

Page 5197: add ",12" after "ref 7" in the text.

Page 5198: (i) two lines below eq 16, replace "**9**" with "4"; (ii) in ref 18, replace "2, 1.5 and 1" with "1, 1.5 and 2"; (iii) column 2, omit "of eq 10" after "the CI wave function[7]".

Page 5200: (i) in the caption for Figure 6, interchange c and d; (ii) in ref 41, replace "P. Passmore" with "J. Passmore".

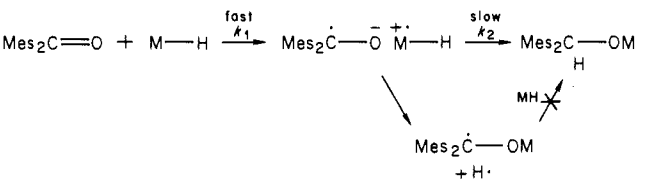
Page 5201: in ref 52, replace "2f" with "2g".

Evidence for an Electron-Transfer Mechanism in the Reduction of Ketones by Main Group Metal Hydrides [*J. Am. Chem. Soc.* **1980**, *102*, 7779]. EUGENE C. ASHBY,* ANIL B. GOEL, and ROBERT N. DEPRIEST, School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

Page 7780: in ref 7 M_2SO_4 should be H_2SO_4.

Page 7780: Scheme I should read as follows.

Scheme I



Accurate and Sensitive Determination, by a New Cobalt-59 Nuclear Magnetic Resonance Method, of Electron Acceptance and Hydrogen Bond Donation by Protic Solvents [*J. Am. Chem. Soc.* **1980**, *102*, 7818–7820]. PIERRE LASZLO* and ARMEL STOCKIS, Institut de Chimie Organique et de Biochimie, Université de Liège, Sart-Tilman, B-4000 Liège, Belgium.

References 14 and 15 have been inadvertently interchanged. They should read: (14) Samo, M.; Yamatera, H.; Hatano, Y. *Chem. Phys. Lett.* **1979**, *60*, 257–260; and (15) Cotton, F. A.; Wilkinson, G. "Advanced Inorganic Chemistry", 3rd ed.; Wiley: New York, 1972.