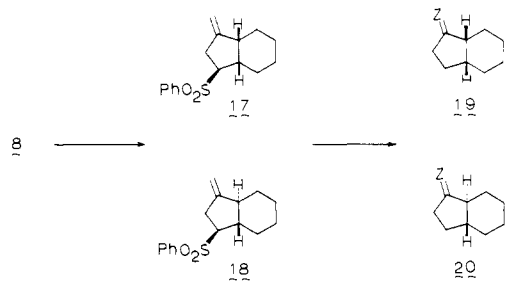
to equilibrate **11** with base led to no change in stereochemistry support the assignments presented.

Subjection of **8** to the same reaction conditions leads to a 70%



yield of the bicyclo[4.3.0]nonanes **17**[7] and **18**[7] in a 2:1 ratio. That the mixture resulted from a mixture of ring-juncture isomers and not from the stereochemistry of the sulfone is demonstrated by desulfonylation (6% Na(Hg), Na_2HPO_4, CH_3OH)[11] to **19a**[7] and **20a**[7] in the same ratio. Ozonolysis (O_3, CH_3OH, CH_2Cl_2, −78 °C) and comparison (spectrally and chromatographically) of the resulting ketone mixture of **19b** and **20b** to an authentic sample[14] assign the major isomer to the cis-fused series and the minor isomer to the trans-fused series. Note that the stereochemistry of the sulfone group in both products faithfully reflects the stereochemistry of the starting olefin.

The reaction is best envisioned in the two-step manner depicted in eq 2. That nucleophilic attack must be initiated by the carbon atom of the TMM–Pd moiety bearing the electron-releasing alkyl substituent is in accord with our earlier work on the methyl-substituted series.[15] The surprising success of the process for formation of the bicyclo[3.3.0]octyl system raises the specter of the initial addition being reversible. Carbon leaving groups in retro-Michael reactions are rare—usually requiring release of strain energy or formation of an exceptionally stabilized anion. Unfortunately, the question of the relative stability of TMM–Pd cannot be addressed at the moment. A more probable explanation lies in the initial addition proceeding preferentially to give the cis adduct in the first step. While steric factors argue against such a proposal, this step does involve conversion of a β-zwitterion-like species (i.e., the TMM–Pd complex) to one with greater separation of charge. Initial formation of a cis five-membered ring minimizes this charge separation. The formation of both isomers in the bicyclo[4.3.0]nonyl system supports this view. Once again, the cis isomer dominates. However, the ability to place the two substituents in a diequatorial arrangement not only can minimize charge separation but also can relieve unfavorable skew interactions. Thus, formation of the trans-fused product begins to compete. Additional evidence favoring this interpretation arises from the failure of **9** to give a bicyclic product since the initial Michael addition requires formation of the unfavorable ten-membered ring. It is interesting to contrast this failure with the facility of palladium-initiated macrocyclizations of allylic acetates to form a very unfavorable ring size.[16] In these latter cases charge neutralization accompanying the cyclization accounts for their successes; in the former case, charge separation must occur and the reaction fails. Fortunately, it is clear that an intramolecular [3 + 2] strategy is feasible in appropriate cases. The facility of forming the desired substrates by utilizing **1** suggests the above may be a very useful strategy in synthesis of multicyclic compounds bearing at least one cyclopentanoid ring.

(14) Larock, R. C.; Dertte, K.; Potter, G. F. *J. Am. Chem. Soc.* **1980**, *102*, 190. The equilibrium ratio of **19b** to **20b** is 3:1. See: House, H. O.; Rasmusson, A. H. *J. Org. Chem.* **1963**, *28*, 31.

(15) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1981**, *103*, 5972. Gordon, D. J.; Fenske, R. F.; Nanninga, T. N.; Trost, B. M. *Ibid.* **1981**, *103*, 5974.

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Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. We thank Englehard Industries and Johnson Matthey and Co. for supplies of palladium salts. D.M.T.C. acknowledges receipt of a Standard Oil of Ohio Fellowship. We also like to acknowledge Professor Gassman for providing spectra of **14** and Professor Larock for spectra and an authentic sample of **19b** and **20b**.

Registry No. 1, 81790-10-5; **2**, 59612-36-1; **3**, 81790-11-6; **4**, 81790-12-7; **5**, 81790-13-8; **6**, 81790-14-9; **7**, 81790-15-0; **8**, 81790-16-1; **9**, 81790-17-2; **11**, 81790-18-3; **12**, 81790-19-4; **13**, 81790-20-7; **14**, 70598-79-7; **15**, 81790-21-8; **17**, 81790-22-9; **18**, 81790-23-0; **19a**, 52775-75-4; **19b**, 2826-65-5; **20a**, 81790-24-1; **20b**, 16783-22-5; lithium (trimethylsilyl)cyanocuprate, 81802-36-0; 2,3-dibromopropene, 513-31-5.

Supplementary Material Available: Spectral data for **1**, **6**, **7**, **8**, **11**, **13**, **17**, and **18** (2 pages). Ordering information is given on any current masthead page.

Synthesis of Jaborosalactone A, B, and D[1]

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Withanolides, a group of naturally occurring steroids with an ergostane-type skeleton, have been isolated from the plants of the *Solanaceae* family.[2a] Several members possess interesting biological activities, mainly antitumor[2b] and insect antifeedant properties.[2c] Their novel structures, which include the highly oxygenated A:B rings and also include the side-chain lactone, have made them an attractive synthetic target. Although several synthetic approaches to the functionalities have been made,[3] a total synthesis has not yet been accomplished.

In this communication, we report the synthesis of jaborosalactone A (**1a**),[4a] B (**1b**),[4a] and D (**1c**)[4b] as a first synthesis of withanolides from a readily available steroid (Scheme I). The key strategy involves the side-chain synthesis in which the correct configuration at C_{22} is generated via the (22*S*)-22,23-epoxide **7**, and the hydroxymethyl unit at C_{25} is introduced into the C_{25} anion equivalent of **9**, the enolate of **11a**.

Commercially available 3β-hydroxy-22,23-bisnorchol-5-enoic acid (**2**) was transformed into the triol diacetate **4**.[5] In four steps **4** was converted to the 1,3-bis(methoxymethyl) (MOM) ether **5** of the 22-olefin in good yield. Generation of the *R* configuration at C_{22} was efficiently accomplished through the transformation of the chiral 22(*S*)-epoxide **7**, which was prepared from **5** by the

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(1) Synthetic Studies of Withanolides. 5. Part 4: Hirayama, M.; Gamoh, K.; Ikekawa, N. *Chem. Lett.* **1982**, 491.

(2) (a) For a review on the withanolides, see: Glotter, E.; Kirson, I.; Lavie, D.; Abraham, A. "Bio-Organic Chemistry"; van Tamelen, E. E., Ed.; Academic Press: New York, 1978; Vol. 2. (b) Shohat, B.; Gitter, S.; Abraham, A.; Lavie, D. *Cancer Chemother. Rep.* **1967**, *51*, 271. (c) Begley, M. J.; Crombie, L.; Ham, P. J.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1976**, 296.

(3) For synthetic approaches to the side-chain moieties, see: Kajikawa, A.; Morisaki, M.; Ikekawa, N. *Tetrahedron Lett.* **1975**, 4135. Ishiguro, M.; Hirayama, M.; Saito, H.; Kajikawa, A.; Ikekawa, N. *Heterocycles* **1981**, *15*, 823. For syntheses of the A:B ring moieties, see: Ishiguro, M.; Kajikawa, A.; Haruyama, T.; Ogura, Y.; Okubayashi, M.; Morisaki, M.; Ikekawa, N. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2295. Weissenberg, M.; Lavie, D.; Glotter, E. *Ibid.* **1977**, 795.

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(5) Fuerst, A.; Labler, L.; Meier, W. Ger. Offen. 1978, 2,746,107; *Chem. Abstr.* **1978**, *89*, 60008f.

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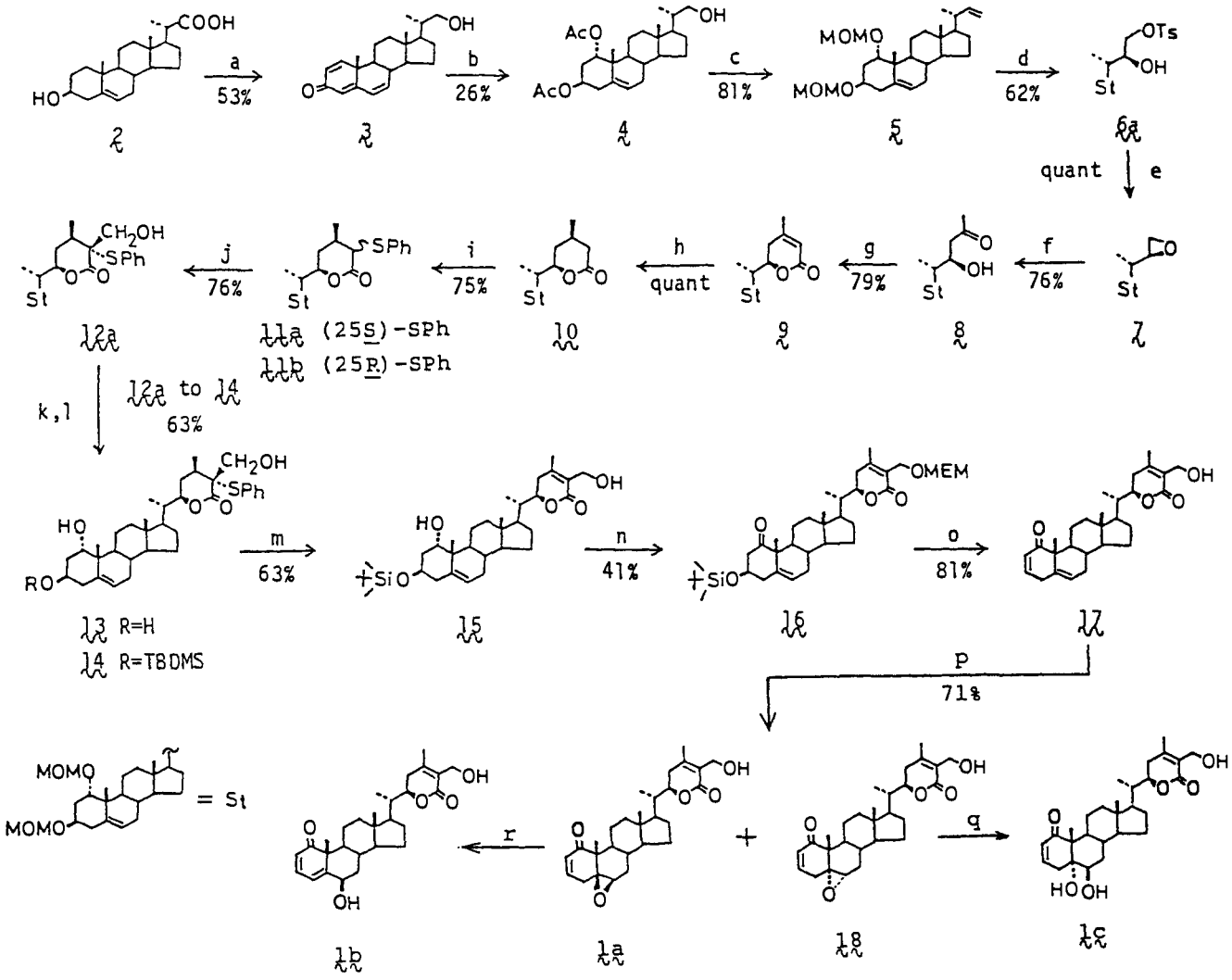
Scheme I. Synthesis of Jaborosalactone A (1a), B (1b), and D (1c)



[a] LAH, THF/4.2 equiv of DDQ, dioxane, reflux. [b] According to ref 5, five steps. [c] PCC, CH_2Cl_2/$Ph_3P{=}CH_2$, ether–THF/NaOH, MeOH–THF/MOMCl, *i*-Pr_2NEt-dioxane. [d] OsO_4, *N*-methylmorpholine oxide, *t*-BuOH–THF–H_2O/*p*-TsCl-Py. [e] K_2CO_3, MeOH. [f] 2-Methyl-1,3-dithiane (BuLi), THF, −78 °C HgO, $BF_3{\cdot}OEt_2$, THF–H_2O, room temperature. [g] $BrCH_2COBr$, ether–Py/$P(OEt)_3$/NaH, THF. [h] H_2 (5% Pd–C), $NaHCO_3$–dioxane. [i] 2 equiv of LICHA, THF, −78 °C/1 equiv of $(PhS)_2$, HMPA–THF, −78 °C. [j] LICHA, THF, −78 °C/CH_2O, THF, −78 °C. [k] aq HCl–THF. [l] TBDMSCl, imidazole–DMF. [m] 1 equiv of *m*-CPBA, $CHCl_3$, −78 °C/neat, 100 °C. [n] MEMCl, *i*-Pr_2NEt–CH_2Cl_2/PDC, DMF. [o] AcOH–H_2O–THF/Ac_2O–Py/Al_2O_3, C_6H_6/H_2SO_4–THF. [p] *m*-CPBA, CH_2Cl_2. [q] 3% aq $HClO_4$–THF. [r] 5% aq KOH–THF.

application of our developed stereoselective epoxidation of steroidal 22-olefins,[6] into 22(*R*)-lactone **9**. Osmium tetraoxide oxidation of **5** followed by tosylation afforded a 5:1 mixture of tosylates **6a** (syrup) and **6b** (mp 83–85 °C). The major isomer **6a**, tentatively assigned as indicated,[7] was converted to the chiral 22,23-epoxide **7**. Regiospecific alkylation of **7** with 2-methyl-1,3-dithiane anion followed by dethioketalization with mercuric oxide–boron trifluoride etherate[8] gave the 22-hydroxy-24-one **8**. According to the strategy developed by McMorris,[9] **8** was transformed into the α,β-unsaturated δ-lactone **9** (mp 149–150 °C). The *R* configuration at C_{22} was determined by the positive Cotton effect at 250 nm ($\Delta\epsilon = +5.87$) in agreement with those of the natural withanolides.[4,10]

So that a hydroxymethyl unit at C_{25} could be introduced, **9** was converted to the C_{25} anion equivalent, the saturated α-phenylthio lactone **11a**. Hydrogenation of **9** proceeded stereospecifically to afford the saturated lactone **10** as a sole product.[11] Sulfenylation of **10** with diphenyl disulfide by inverse quench[12] gave a 3:2 mixture of sulfides **11a**[13] (mp 140–141 °C) and **11b**[13] (mp 90–92 °C). Conversion of **11b** to **11a** with lithium isopropylcyclohexylamide (LICHA) supported structures epimeric at C_{25}. Treatment of the anion of **11a** with excess monomeric formaldehyde gave a 9:1 mixture of stereoisomers **12a**[13] (syrup) and **12b**[13] (mp 179–181 °C). It was concluded from the following experiment that the desired stereochemical requirement for facile desulfenylation was filled by the major 25(*R*) isomer **12a**.[12,14] Cleavage of the 1,3-bis(MOM) ether of **12a** with acid followed

(6) Ishiguro, M.; Ikekawa, N. *Chem. Pharm. Bull.* **1975**, *23*, 2860. Ishiguro, M.; Saito, H.; Sakamoto, A.; Ikekawa, N. *Ibid.* **1978**, *26*, 3715.

(7) The assigned structure was confirmed by the successful transformation into **9**.

(8) Vedejs, E.; Fuchs, P. L. *J. Org. Chem.* **1971**, *36*, 366.

(9) Weihe, G. R.; McMorris, T. C. *J. Org. Chem.* **1978**, *43*, 3942.

(10) (a) Snatzke, G. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 14. (b) Lavie, D.; Kirson, I.; Glotter, E.; Snatzke, G. *Tetrahedron* **1970**, *26*, 2221.

(11) **10**: partial ^1H NMR (100 MHz; $CDCl_3$) δ 4.36 (1 H, dt, J = 3, 12 Hz, $C_{22}H$), 2.66 (1 H, dd, J = 10, 21 Hz, quasi-axial $C_{25}H$; collapsing to a doublet ($J \approx 10$ Hz) upon irradiation at 2.02). This spectrum suggests that **10** possesses the half-chair conformation with *R* configuration at C_{24}. This result is in agreement with that of the reported hydrogenation of withaferin A diacetate. See ref 10b.

(12) Trost, B. M.; Salzmann, T. N.; Horii, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

(13) Partial ^1H NMR δ: (**11a**) 3.28 (1 H, d, J = 8 Hz, $C_{25}H$); (**11b**) 3.70 (1 H, d, J = 5 Hz, $C_{25}H$); (**12a**) 3.68, 3.88 (4 H, m, C_1H, C_3H, $C_{27}H_2$), 4.84 (1 H, dt, $J \approx 3$, 11 Hz, $C_{22}H$); (**12b**) 3.64, 3.94 (4 H, m, C_1H, C_3H, $C_{27}H_2$), 4.43 (1 H, dt, J = 3, 11 Hz, $C_{22}H$); (**18**) 3.05 (1 H, d, J = 5 Hz, C_6H), 5.96 (1 H, ddd, J = 0.7, 3, 10 Hz, C_2H), 6.72 (1 H, ddd, J = 2.5, 5, 10 Hz, C_3H).

(14) In the similar treatment of the minor 25(*S*)-isomer **12b**, the desulfenylated product could not be obtained.

by silylation with *tert*-butyldimethylsilyl chloride (TBDMSCl) at room temperature afforded the 3-TBDMS ether **14** (mp 230–233 °C) in good yield. Fortunately, each of the three hydroxy groups in the 1,3,27-triol **13** could be distinguished, because the primary hydroxy group at C_{27} was not silylated under this condition probably due to the steric effect. Oxidation of **14** with *m*-CPBA to the sulfoxide followed by desulfenylation gave the unsaturated δ-lactone **15** (mp 197–198 °C), which had the same side-chain moiety as those of jaborosalactones.

The final problem of the construction of the A:B rings was accomplished as follows. Selective protection of the hydroxy group at C_{27} with methoxyethoxymethyl chloride (MEMCl) was followed by oxidation with pyridium dichromate (PDC) at C_1 to afford **16**, which was transformed into the 2,5-dien-1-one **17** in four steps. Epoxidation of **17** with *m*-CPBA gave a 1:2.5 mixture of two isomeric 5,6-epoxides, and subsequent separation by preparative TLC gave jaborosalactone A (**1a**) as the minor and less polar 5β,6β-epoxide. Treatment of the major and more polar 5α,6α-epoxide **18**[13] (mp 254–256 °C) with 3% perchloric acid yielded jaborosalactone D (**1c**). The reported isomerization of **1a** with base[4a] or dehydration of **1c** with *p*-toluenesulfonic acid gave jaborosalactone B (**1b**). The physical and spectral data of the synthesized samples were identical with the published data.[4] In addition, ^{1}H NMR,[15] HPLC, and CD data comparison of synthetic and natural materials of jaborosalactone A and B[16] showed no differences.

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Registry No. 1a, 5788-94-3; **1b**, 6105-16-4; **1c**, 19891-82-8; **2**, 566-77-8; **3**, 66875-12-5; **4**, 66875-21-6; **5**, 81426-78-0; **6a**, 81426-79-1; **6b**, 81897-53-2; **7**, 81874-38-6; **8**, 81426-80-4; **9**, 81426-81-5; **10**, 81874-39-7; **11a**, 81426-87-1; **11b**, 81426-82-6; **12a**, 81874-40-0; **12b**, 81874-45-5; **13**, 81874-41-1; **14**, 81967-91-1; **15**, 81874-42-2; **16**, 81874-43-3; **17**, 81874-44-4; **18**, 81939-02-8; $BrCH_2COBr$, 598-21-0.

(15) We thank Dr. M. Fukui, The Institute of Physical and Chemical Research, for measurement of ^{1}H NMR (400 MHz) spectra.

(16) We express our appreciation to Professor I. Kirson, The Hebrew University of Jerusalem, for sending us the authentic samples of jaborosalactone A and B.

Bis(2,4-dimethylpentadienyl)titanium: An "Open Titanocene"

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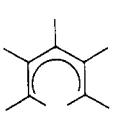
Two of the most useful ligands in organometallic chemistry are the closed five-membered cyclopentadienyl ligand and the open three-membered allyl ligand.[1] Very much neglected has been the chemistry of the related open five-membered pentadienyl ligand (I).[2] Various considerations have led us to the conclusion that



I

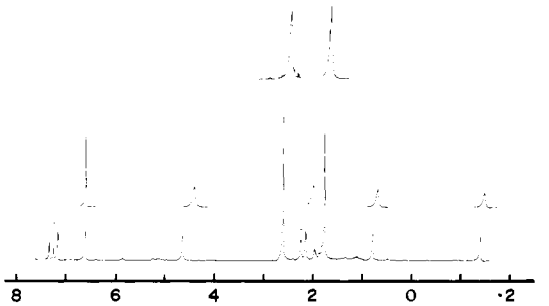


Figure 1. ^{1}H NMR spectra of $(2,4\text{-}C_7H_{11})_2Ti$ at −73 °C (below) and room temperature (above) in toluene-d_8.

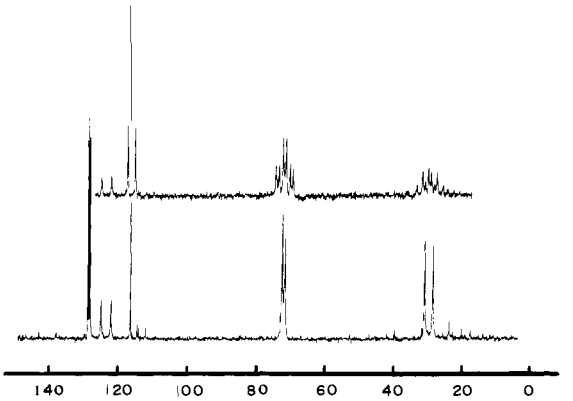


Figure 2. Proton-decoupled (below) and -coupled (above) ^{13}C NMR spectra of $(2,4\text{-}C_7H_{11})_2Ti$ at room temperature in benzene-d_6.

such a ligand should be capable of imparting both stability and catalytic activity into its metal complexes, and as a result we have been pursuing the chemistry of such systems.[3] Of initial interest have been bis(pentadienyl)metal complexes, which may be regarded essentially as "open metallocenes". Such complexes should allow detailed physical and chemical comparisons between the pentadienyl and cyclopentadienyl ligands, as well as providing a great deal of information for open-ligand systems (e.g., allyl) in general, which is not available primarily due to the very low stabilities of most homoleptic metal–allyl complexes. Thus, we have already reported such open sandwich compounds of vanadium, chromium, manganese, and iron.[3] However, perhaps the most intricate metallocene chemistry has been exhibited by titanium, for which the simple sandwich structure $Ti(C_5H_5)_2$ is well known to be quite unstable relative to various other (often extremely reactive) forms, which may contain fulvalene, $\eta^1,\eta^5\text{-}C_5H_4$, hydride, and perhaps other ligands as well.[4] Indeed, even decamethyltitanocene possesses only limited stability.[5] Because of the rich variety of chemistry demonstrated by the titanocene systems, it was anticipated that the chemistry of open-titanocene

(1) Collman, J. P.; Hegedus, L. S. "Principles and Applications of Organotransition Metal Chemistry"; University Science Books: Mill Valley, CA, 1980.

(2) Some examples: (a) Mahler, J. E.; Pettit, R. *J. Am. Chem. Soc.* **1962**, *84*, 1511. (b) Giannini, U.; Pellino, E.; Lachi, M. P. *J. Organomet. Chem.* **1968**, *12*, 551. (c) Rienacker, R.; Yoshiura, H. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 677. (d) Krüger, C. *Ibid.* **1969**, *8*, 678. (e) Seyferth, D.; Goldman, E. W.; Pornet, J. *J. Organomet. Chem.* **1981**, *208*, 189.

(3) (a) Wilson, D. R.; DiLullo, A. A.; Ernst, R. D. *J. Am. Chem. Soc.* **1980**, *102*, 5928. (b) Wilson, D. R.; Liu, J.-Z.; Ernst, R. D. *Ibid.* **1982**, *104*, 1120. (c) Ernst, R. D.; Cymbaluk, T. H. *Organometallics* **1982**, *1*, 708. (d) Ernst, R. D.; Campana, C. F.; Wilson, D. R.; Liu, J.-Z., to be submitted for publication. (e) Bohm, M. C.; Eckert-Maksič, M.; Ernst, R. D.; Wilson, D. R.; Gleiter, R. *J. Am. Chem. Soc.* **1982**, *104*, 2699.

(4) (a) Bercaw, J. E.; Brintzinger, H. H. *J. Am. Chem. Soc.* **1969**, *91*, 7301. (b) Brintzinger, H. H.; Bercaw, J. E. *Ibid.* **1970**, *92*, 6182. (c) Bercaw, J. E.; Brintzinger, H. H. *Ibid.* **1971**, *93*, 2045. (d) Marvich, R. H.; Brintzinger, H. H. *Ibid.* **1971**, *93*, 2046. (e) Bercaw, J. E.; Marvich, R. H.; Bell, L. G.; Brintzinger, H. H. *Ibid.* **1972**, *94*, 1219. (f) Alt. H.; Rausch, M. D. *Ibid.* **1974**, *96*, 5936. (g) Guggenberger, L. J.; Tebbe, F. N. *Ibid.* **1976**, *98*, 4137. (h) Pez, G. P. *Ibid.* **1976**, *98*, 8072. (i) Pez, G. P.; Kwan, S. C. *Ibid.* **1976**, *98*, 8079. (j) Armor, J. N. *Inorg. Chem.* **1978**, *17*, 203. (k) Armor, J. N. *Ibid.* **1978**, *17*, 213. (l) Pez, G. P. *J. Chem. Soc., Chem. Commun.* **1972**, 481. (m) Peng, M.; Brubaker, C. H., Jr. *Inorg. Chim. Acta* **1978**, *26*, 231. (n) Pez, G. P.; Armor, J. N. In "Advances in Organometallic Chemistry"; West, R., Stone, F. G. A., Eds.; Academis Press: New York, 1981; Vol. 19, p 1.

(5) (a) The compound actually exists in equilibrium with $(\eta^5\text{-}C_5(CH_3)_5)(\eta^6\text{-}C_5(CH_3)_4CH_2)TiH$ and decomposes slightly above room temperature.[5b] (b) Bercaw, J. E. *J. Am. Chem. Soc.* **1974**, *96*, 5087.

0002-7863/82/1504-3737$01.25/0