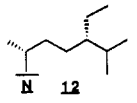
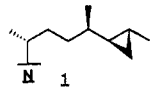
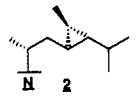
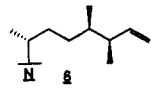
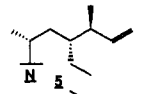
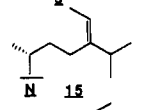
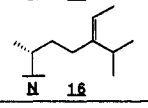
Table I. Results of Feeding Experiment with *P. ficiformis* (8.8×10^7 dpm [3-^{3}H]Clionasterol (**12**))

sterols	recovered radioact., dpm (% recovered)	sp act., dpm/mg
 **12**	7.4×10^6 (8.4%)	2.8×10^6
 **1**	4.4×10^6 (5.0%)	2.3×10^5
 **2**	6.0×10^5 (0.7%)	2.2×10^5
 **6**	7.1×10^4 (0.08%)	2.5×10^5
 **5**	2.0×10^4 (0.02%)	(not determined)
 **15**	1.0×10^4 (0.01%)	2.5×10^4
 **16**	0	0

tonated cyclopropane (**7**) to produce (Figure 1) the sponge sterols, or, in the yeast mutant, capture a hydroxyl group to yield the 23-hydroxy sterol (**13**).

When [3-^{3}H]clionasterol (**12**) was fed to *Petrosia ficiformis*, ca. 40% of the recovered radioactivity was found by reverse-phase HPLC in the cyclopropyl sterols, petrosterol (**1**) and dihydrocalysterol (**2**, Table I).[13] The remainder was in recovered starting material. The radiochemical purity of petrosterol (**1**) was checked by reverse-phase HPLC using a second solvent system and by hydrogenation to petrostanol;[6b] all of the radioactivity coeluted with the reduced sterol on HPLC. The purity of the other radioactive products was checked in the same way. Upon closer examination, small amounts of radioactivity were found to coincide with certain minor sterols present in the sponge, ficisterol (**5**) and 26(29)-dehydroaplysterol (**6**). These have previously been proposed to arise via the protonated cyclopropane intermediate **7** (Figure 1).[8] Fucosterol (**15**), but not isofucosterol (**16**), was also found to contain radioactivity. The specific activities of petrosterol (**1**), dihydrocalysterol (**2**), 26(29)-dehydroaplysterol (**6**), and ficisterol (**5**) were all approximately equal (Table I), strongly suggesting that these all arise from the partitioning of a common enzymatic reaction intermediate. The specific activity of fucosterol (**15**) was lower. This is consistent with either dilution by dietary sterol, since fucosterol (**15**) is a common sterol in the marine environment, or with the existence of a different pathway.

To our knowledge, this is the first time a saturated alkyl group has been shown to be enzymatically converted to a cyclopropane. It is likely that the other unusual sterols (e.g., **3**, **4**) associated with the Haplosclerida also arise through the action of similar errant Δ^{22}-desaturases. The irony that these unique sponge sterols should result from the sponge's inability to form poriferasterol (**14a**, Figure 4) (Porifera = sponges) has not escaped us.

Acknowledgment. We thank the NIH (Grant No. GM-06840) for financial support; Dr. Guido Sodano, Mr. Antonio Trabucco, and Mr. Antonio Crispino (Institute for the Chemistry of Biologically Interesting Molecules, Arco Felice, Italy) for their assistance in performing the feeding experiment at the Naples Zoological Station; and Dr. Robert Simoni (Stanford University) for access to his scintillation counter.

(13) For general methods, see ref 7a.

Metallacycle Annelation: Reaction of a Metallacycle α-Substituent and a Vinylidene Ligand To Give a Bicyclic Metallalactone Complex

Joseph M. O'Connor,* Lin Pu, and Raj K. Chadha

Department of Chemistry (0506)
University of California at San Diego
La Jolla, California 92093-0506

Received August 31, 1990

Metallacycle complexes are widely employed intermediates for an impressive array of cyclization chemistry.[1] Methodology for controlled elaboration of metallacycles will greatly expand the utility of this compound class. We recently reported that Ir(CR=CRCR=CR)$(PPh_3)_2(CH_3CN)_2^+BF_4^-$ (**1**; R = CO_2CH_3) undergoes reaction with methyl propiolate in the presence of $^{18}OH_2$ to give the carbonyl complex **2** and methyl acetate (Scheme I).[2] In order to explain the location of the ^{18}O label in the α-methoxycarbonyl metallacycle substituent of **2**, we proposed intramolecular transfer of the original α-methoxycarbonyl oxygen to an intermediate vinylidene ligand. This mechanistic hypothesis, as well as an earlier observation of a surprising metallacycle annelation of unknown mechanism,[3] indicated promise for the design and implementation of a new class of metallacycle annelation reaction. We now report synthetic and mechanistic results on such an annelation strategy, including the conversion of Ir(CR=CRCR=CR)$(PPh_3)_2(L)(CO)^+BF_4^-$ (R = CO_2CH_3, L = CH_3CN, OH_2)[2,4] (**3**-L) and phenylacetylene to a stable bicyclic metallalactone complex, **4**. Mechanistic insight into the formation of **4** is obtained from oxygen-18 and deuterium labeling studies as well as independent synthesis from a metallacycle–acetylide complex.

In wet chloroform solution the aquo complex Ir(CR=CRCR=CR)$(PPh_3)_2(OH_2)(CO)^+BF_4^-$ (**3**-OH_2, R = CO_2CH_3, 0.049 mmol, 9.3 mM) and phenylacetylene (20 μL, 0.182 mmol) generate the bicyclic metallalactone **4** in 91% yield (24 h at 23 °C).[5] The ^{1}H NMR spectrum ($CDCl_3$) of **4** establishes the presence of only three methyl groups [δ 3.70 (s, 3 H), 3.40 (s, 3 H), and 3.23 (s, 3 H)]. The observation of a single vinyl hydrogen resonance at δ 5.53 indicates a single alkene isomer of unknown configuration. In the ^{13}C NMR spectrum (126 MHz, $CDCl_3$), the carbon resonances of the exocyclic alkene are observed at 145.1 (td, $^2J_{CH}$ = 11.8 Hz, J_{CP} = 9.2 Hz, Ir*C*=CHPh) and 125.5 (br d, $^1J_{CH}$ = 152 Hz, IrC=*C*HPh) ppm. The lactone carbonyl carbon at 172.1 (s) ppm is distinguished from the methoxycarbonyl carbons by the absence of a $^3J_{CH}$ coupling. In the $^{31}P\{^1H\}$ NMR spectrum, a singlet at −10.0 ppm requires a plane of symmetry that bisects the phosphorus–phosphorus axis and contains the ring atoms.

In order to establish the mechanism for this new cyclization reaction, we carried out the reaction of **3**-CH_3CN and phenylacetylene in the presence of $^{18}OH_2$ at 50 °C ($CDCl_3$) to give **4**-O. A $^{13}C\{^1H\}$ NMR spectrum of the sample was taken, and **4** was then added. A $^{13}C\{^1H\}$ NMR spectrum (126 MHz, $CDCl_3$) of the ~1:2 mixture of **4**:**4**-O exhibited a 4.3-Hz upfield isotopic shift for a single resonance at 171.9 ppm [*C*(=O)OC(=CHPh)Ir, **4**].[6] Thus, the oxygen-18 from $^{18}OH_2$ was selectively incorporated

(1) (a) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081. (b) Lindner, E. *Adv. Heterocycl. Chem.* **1986**, *39*, 237. (c) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539. (d) Chappell, S. D.; Cole-Hamilton, D. J. *Polyhedron* **1982**, *1*, 739.

(2) O'Connor, J. M.; Pu, L. *J. Am. Chem. Soc.* **1990**, *112*, 9013–9015.

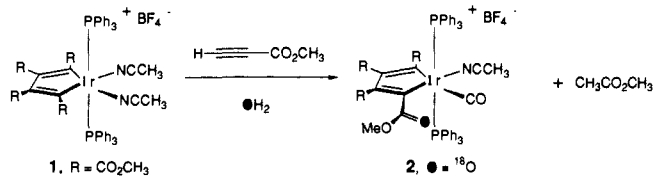
(3) O'Connor, J. M.; Pu, L.; Chadha, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 543.

(4) O'Connor, J. M.; Pu, L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1987**, *109*, 7578.

(5) Complete characterization data for **4** and **6** is provided as supplementary material.

0002-7863/90/1512-9627$02.50/0

Scheme I



1, R = CO_2CH_3 2, • = ^{18}O

into the carbonyl carbon of the metallalactone ring in **4**-O. The **4**:**4**-O mixture was heated in $CDCl_3$ containing $^{16}OH_2$ for 50 h at 50 °C, and no $^{16}O/^{18}O$ exchange was observed. When the reaction of **3**-CH_3CN and phenylacetylene is monitored by ^1H NMR spectroscopy, the acetylide **6** is observed as a transient species. In the presence of D_2O, the product **4** has deuterium at the vinyl hydrogen site. Heating solutions of **4** in the presence of D_2O does not lead to deuterium incorporation. The observed deuterium incorporation may be indicative of an equilibrium between **6** and an unobserved vinylidene intermediate **5**, under the reaction conditions. These results are consistent with a mechanism that involves vinylidene **5** and hemiortho ester **7**, as shown in Scheme II.[7]

In an effort to trap the proposed vinylidene intermediate **5**, we carried out the reaction of **3**-CH_3CN and phenylacetylene in the presence of NaOH. After 24 h at 50 °C, an 88% yield of the metallacycle–acetylide complex **6** was observed by ^1H NMR spectroscopy (Scheme II).[5] The formation of **6** presumably involves initial formation of **5**[8] followed by rapid deprotonation of the vinylidene ligand.[9-11] Access to **6** provides an alternative route to vinylidene intermediate **5**. Thus, protonation of **6** with HCl in chloroform-d_1 solution results in quantitative conversion to **4**, as determined by ^1H NMR spectroscopy.

In order to model the solid-state structure of the proposed vinylidene intermediate **5**, we performed an X-ray crystallographic analysis on **6** (Figure 1).[12] The C(4)–Ir–C(2) angle is 98.6°, and the nonbonded O(2)–C(2) distance is 3.25 Å. For comparison, the C(7)–Ir–C(1) angle is 100.2°, with an O(8)–C(1) nonbonded distance of 3.15 Å. Rotation (molecular modeling) about the C(4)–C(8) bond brings O(2) within a 2.86-Å distance of C(2). A space-filling model of **6** indicates that the electrophilic carbon C(2) (and therefore the α-vinylidene carbon in **5**) is effectively buried within the coordination sphere, unlike C(8), and is therefore much less accessible to attack by water than the α-methoxycarbonyl carbon.

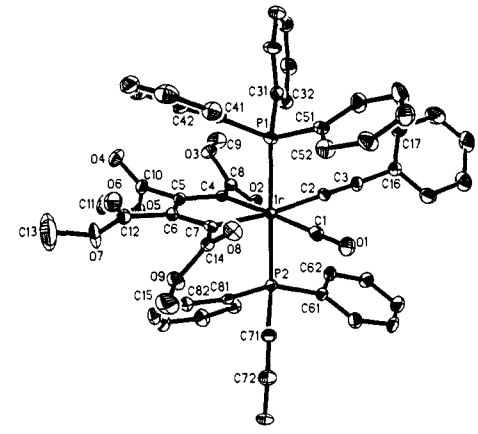
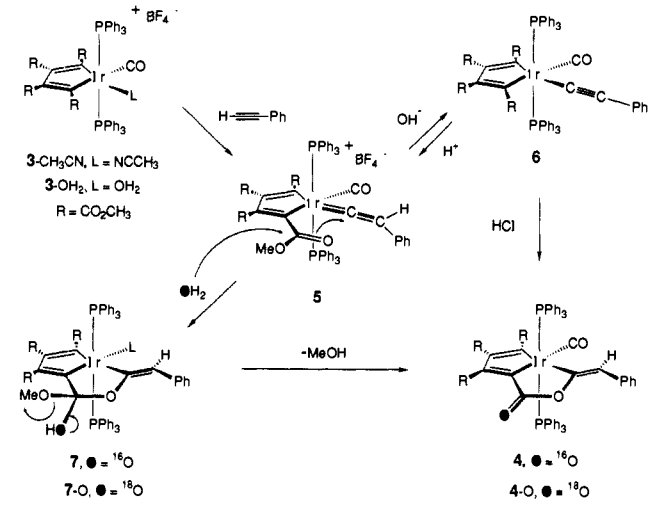


Figure 1. Molecular structure and labeling scheme for **6** bond distances (Å) and angles (deg): Ir–C(1), 1.914 (8); Ir–C(2), 2.056 (9); Ir–C(4), 2.085 (7); Ir–C(7), 2.081 (8); C(2)–C(3), 1.198 (13); C(2)–Ir–C(4), 98.6 (3); C(1)–Ir–C(2), 83.6 (4); C(1)–Ir–C(7), 100.2 (3); C(4)–Ir–C(7), 77.8 (3).

Scheme II



Formation of bicyclo metallalactone **4** represents a new metallacycle annelation reaction involving a metallacycle α-substituent and an adjacent ligand.[13] The mechanistic studies reported here are consistent with our previously proposed mechanism for alkyne cleavage chemistry (**1** to **2**). Further studies directed toward the implementation of this annelation strategy are underway.

Acknowledgment. Support by the National Science Foundation (CHE-9005973) is gratefully acknowledged. The NMR spectrometer utilized in this work was funded by the National Science Foundation (CHE-8814866) and the National Institutes of Health (RR-04733). We also thank Dr. Ron New of the University of California, Riverside Mass Spectrometry Center, for obtaining the mass spectral analyses. We are very grateful to Johnson-Matthey for a generous loan of precious metals.

Supplementary Material Available: Full spectroscopic and analytical data for compounds **4** and **6** and listings of fractional coordinates, bond distances, bond angles, hydrogen atom coordinates, and thermal parameters for **6** (8 pages); table of observed and calculated structure factors for **6** (27 pages). Ordering information is given on any current masthead page.

(6) In particular, the vinyl carbon resonance at δ 145.1 did not exhibit an isotopic shift. FAB mass spectral analysis of the initial mixture of **4**-O and **3**-CH_3CN indicates 92(±10)% ^{18}O incorporation [*m/e* 1119 (M^+, **4**-O)]. The large error in the % label is due to inherent limitations in the FAB method of mass spectral analysis.

(7) Methanol formation is observed by ^1H NMR spectroscopy in the conversion of **3** to **4**.

(8) Bruce, M. I. *Pure Appl. Chem.* **1986**, *58*, 553 and references therein.

(9) Bruce, M. I.; Swincer, A. G. *Adv. Organomet. Chem.* **1983**, *22*, 59 and references therein.

(10) Davidson, A.; Selegue, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 7763.

(11) Senn, D. R.; Wong, A.; Patton, A. T.; Marsi, M.; Strouse, C. E.; Gladysz, J. A. *J. Am. Chem. Soc.* **1988**, *110*, 6096 and references therein.

(12) Crystal data for **6** (296 K): $C_{59}H_{49}O_9P_2Cl_6Ir$, triclinic $P\bar{1}$, a = 13.352 (6) Å, b = 13.323 (0) Å, c = 18.385 (9) Å, α = 76.350 (10)°, β = 72.290 (0)°, γ = 68.180 (10)°, V = 2864 (2) Å^3, Z = 2, D(calcd) = 1.587 g/cm^3, μ = 2.712 mm^{-1}. A 0.08 × 0.17 × 0.28 mm specimen was used for data collection (Siemens R3m/V, 4.0° ≤ 2θ ≤ 45.0°, Mo Kα). Of 7494 reflections collected, 7494 were independent (R_{int} = 0.00%) and 5769 with $F > 6.0\sigma(F)$ were considered observed and corrected for absorption by using a face-indexed numerical method. (T_{min}/T_{max} = 0.6156/0.8204). The iridium atom was located by a heavy-atom method. With all non-hydrogen atoms anisotropically refined and hydrogen atoms included in ideal positions with U fixed at 0.08 Å^2: $R(F)$ = 3.95%, $R(wF)$ = 5.04%. GOF = 1.15, Δ/σ = 2.947, $\Delta(\rho)$ = 1.90 e Å^{-3}. Computer programs and sources of scattering factors are in the SHELXTL program library (Siemens Corp., Madison, WI).

(13) For examples of intramolecular attack of a ligand at an adjacent vinylidene ligand: (a) Adams, R. D.; Davison, A.; Selegue, J. P. *J. Am. Chem. Soc.* **1979**, *101*, 7232. (b) Stack, J. G.; Simpson, R. D.; Hollander, F. J.; Bergman, R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1990**, *112*, 2716.