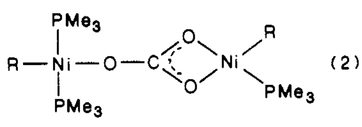
$2Ni(CH_2CMe_2\text{-}o\text{-}C_6H_4)(PMe_3)_2 + CO_2 + H_2O \longrightarrow$

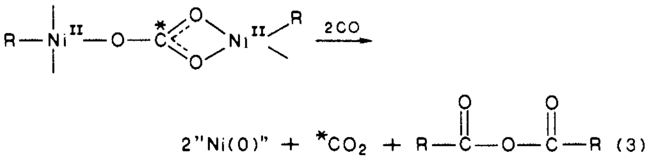


2, R = CH_2CMe_2Ph

CO_2 insertion product into the Ni–aryl carbon bond, is obtained. Complex **3** exhibits a strong IR absorption[12] at ca. 1610 cm^{-1} for the uncoordinated C=O group. The existence of the seven-member nickelalactone unit in the molecule of this compound has been confirmed by X-ray crystallography.[13] A perspective view of the molecular geometry, giving the atom-labeling scheme, is presented in Figure 1, which also includes some important bonding parameters.

The reaction of formaldehyde with transition-metal complexes, and in particular formaldehyde insertion into M–L bonds, is receiving increasing attention in view of the intermediary role played by this molecule in CO reduction.[15] Both the insertion of the CH_2O unit into M–H bonds[16] and the related insertion into M–C bonds, which has been suggested[3a] as a possible propagation step in Fischer–Tropsch chemistry, are still rather uncommon reactions. Addition of aqueous formaldehyde, or preferably paraformaldehyde, to tetrahydrofuran solutions of **1** causes insertion of the CH_2O unit into the *nickel–carbon alkyl bond*, with formation of the oxynickelacycloheptene complex **4**.[17]

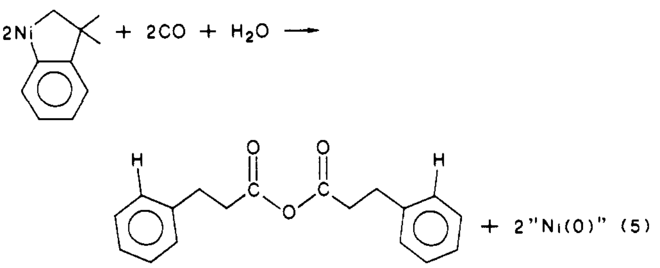
Several organic materials can be derived, in virtually quantitative yields (by NMR spectroscopy), from complexes **1**–**4** by carbonylation. Thus, **1** produces the cyclic ketone **5**, while **3** and **4** afford anhydride **6** and lactone **7**, respectively. Interestingly, the reaction of the carbonate **2** with carbon monoxide takes place with reduction to Ni(0) ($Ni(CO)_2(PMe_3)_2$ plus $Ni(CO)_3(PMe_3)$), formation of anhydride **8**, and evolution of carbon dioxide (eq 3).



Isotopic labeling studies using complex **2**, ^{13}C enriched in the carbonate ligand, clearly demonstrate that the evolved CO_2 derives exclusively from the carbonate group. In a formal sense, eq 3 represents a metal-promoted oxidative conproportionation of carbonate and carbonyl ligands to produce two molecules of carbon dioxide (eq 4). One of these is evolved as free CO_2 while the

$$CO_3^{2-} + CO - 2e = 2CO_2 \qquad (4)$$

second is "functionalized" into the anhydride functionality. Although the opposite reaction, namely, reductive disproportionation of carbon dioxide, is a commonly observed process in transition-metal–carbon dioxide chemistry, to the best of our knowledge eq 3 represents the first example of a carbonate and a carbon monoxide conproportionation induced by a transition-metal complex.[18] Moreover, the simultaneous consideration of eq 2 and 3 reveals that the overall process is a CO_2-mediated hydrocarbonylation of **1** to produce anhydride **8**, as in eq 5.



Further studies on this and related carbonate complexes are in progress to ascertain the generality of this reaction and its potential synthetic applicability.

Acknowledgment. Generous support (to E.C. and E.G.-P.) by the Comisión Asesora de Investigación Científica y Técnica (CAICYT) is very gratefully acknowledged. P.P. and M.P. acknowledge research grants by the Comisión Asesora de Investigación Científica y Técnica (CAICYT) and the Ministerio de Educación y Ciencia (MEC).

Supplementary Material Available: Tables of final fractional coordinates, thermal parameters, and bond distances and angles for **3** (4 pages); table of observed and calculated structure factors for **3** (22 pages). Ordering information is given on any current masthead page.

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(12) Compound **3** seems to exist in two interconvertible forms displaying νC=O at 1610 and 1580 cm^{-1}.

(13) Crystal data for **3**, $C_{17}H_{30}P_2O_2Ni$: M_r = 387.08, orthorhombic, space group $P_{2_12_12_1}$; a = 10.139 (3) Å, b = 10.543 (2) Å, c = 18.665 (3) Å v = 1995.2 (8) Å^3, Z = 4, D_{calcd} = 1.29 g cm^3, $F(000)$ = 824, μ (Mo Kα) = 11.4 cm^{-1}. A yellow prismatic crystal (0.5 × 0.3 × 0.2 mm) was sealed under N_2 in a glass capillary, and data were collected on a Enraf-Nonius CAD4-F diffractometer. The structure was solved by heavy atom methods; 3267 independent reflections were measured of which 2020 were considered observed after the criterion $I > 3\sigma(I)$ and used in the refinement with anisotropic parameters for all non-H atoms except the methyl carbons attached to phosphorus (2). Unit weights were used (no trend in ΔF vs. F_o or sin θ/λ was observed), and at convergence, R_F = 0.067. An absorption correction was applied.[14]

(14) Walker, N.; Stuart, D. *Acta Crystallogr., Sect. A* **1983**, *A39*, 158.

(15) Muetterties, E. L.; Stein, J. *Chem. Rev.* **1979**, *79*, 479. Herrmann, W. A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 117.

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(17) A solution of **1** (1.56 g, ca. 4.55 mmol) in THF (40 mL) is stirred at room temperature with an excess of solid paraformaldehyde for ca. 4 h. The yellow suspension obtained is evaporated to dryness. Crystallization from Et_2O/petroleum ether (1:1 mixture) at −20 °C afforded **4** as yellow microcrystals in ca. 80% yield. This compound exists in solution in two isomeric forms in ca. 2:1 ratio. This possibly arises from the relative positions of the oxyalkyl chains with respect to the Ni_2O_2 ring. Some spectroscopic data corresponding to the major isomer are as follows: $^{31}P\{^1H\}$ NMR (C_6D_6, 21 °C) δ −12.7 s; $^{13}C\{^1H\}$ NMR (C_6D_6, 21 °C) δ 13.7 (d, PMe_3, $^1J_{CP}$ = 28 Hz), 31.6, 35.2 (s, diastereotopics CMe_2), 37.7 (s, CMe$_2$), 50.4 (s, CCH_2), 65.5 (s, OCH_2), 147.8 (d, Ar C bound to Ni, $^2J_{CP}$ = 42.1 Hz). M_r (cryoscopically, C_6H_6), calcd for $C_{28}H_{46}O_2P_2Ni_2$, 593; found, 530. Anal. Calcd for $C_{28}H_{46}O_2P_2Ni_2$: C, 56.6; H, 7.7. Found: C, 56.4; H, 7.7.

(18) Organic allyl alkyl carbonates are known to undergo a Pd-catalyzed decarboxilation–carbonylation process to yield unsaturated esters. Tsuji, J.; Sato, K.; Okumoto, H. *J. Org. Chem.* **1984**, *49*, 1341.

Inside–Outside Stereoisomerism: The Synthesis of *trans*-Bicyclo[5.3.1]undecan-11-one[1]

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We have reported that the intramolecular photoaddition of dioxolenones to alkenes, i.e., **1** → **3**, leads to the formation of six-, seven- and eight-membered rings in good yield.[5] We describe

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[1] Winkler, J. D. Presented in part at the 190th National Meeting of the American Chemical Society, Chicago, IL, Sept 8–13, 1985; paper ORGN 205.

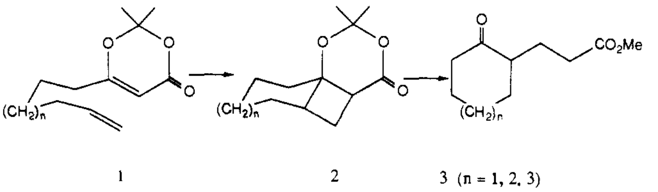
[2] Recipient of a Merck Grant for Faculty Development, 1985–1986.

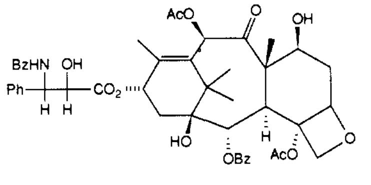
[3] National Institutes of Health Predoctoral Trainee (GM07148).

[4] Author to whom correspondence regarding the X-ray structure of 11 should be addressed.

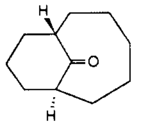
0002-7863/86/1508-6425$01.50/0

Scheme I



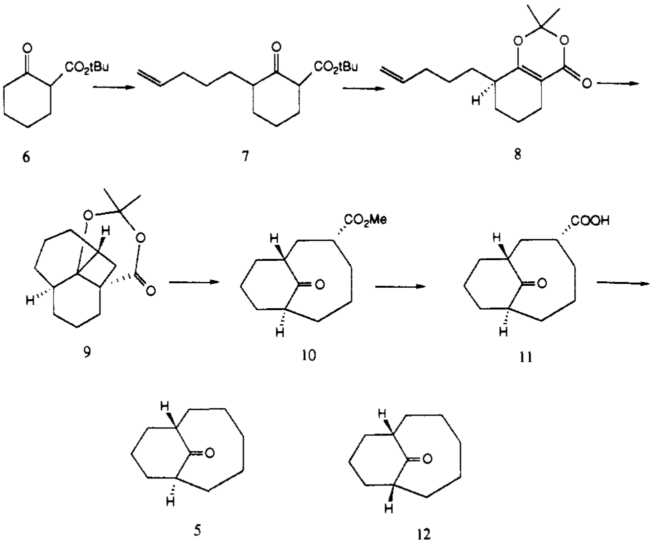


4



5

Scheme II



Scheme III

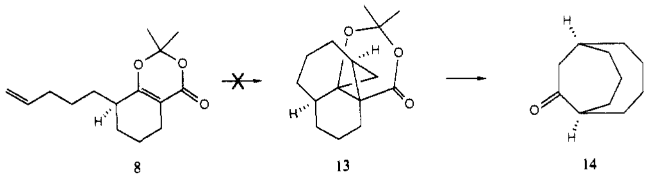
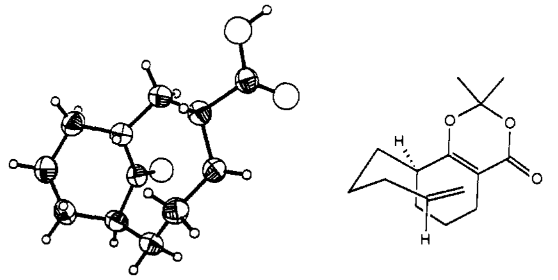


Chart I



herein the application of this reaction to the synthesis of the bicyclo[5.3.1]undecane ring system, an important structural feature of the taxane diterpenes, of which taxol (**4**)[6] has been found to exhibit significant antitumor properties.[7] The stereochemistry of the bicyclo[5.3.1]undecane produced in the intramolecular dioxolenone photocycloaddition is trans-bridged, making **5** the smallest known bicyclic cycloalkane to exhibit inside–outside stereoisomerism[8] (Scheme I).

The photosubstrate **8** was prepared as outlined in Scheme II. Dianion alkylation[10] of *tert*-butyl cyclohexanone-2-carboxylate[11] with 4-pentenyl iodide (89% yield), followed by dioxolenone formation (2 equiv of trifluoroacetic anhydride, 25 equiv of trifluoroacetic acid, acetone, 25 °C, 59% yield)[12] provided **8**. Irradiation of **8** (0.02 M in 1:9 acetone/acetonitrile; Pyrex immersion well; 0 °C) for 4 h produced photoadduct 9, which was directly submitted to the fragmentation conditions (0.1 equiv of *p*-TsOH/methanol/reflux/18 h) that we have previously described[5] to provide **10** in 80% overall yield. The cycloundecanonecarboxylic acid ester **10** was characterized by ^{1}H NMR, IR, and EI-MS.[13] In an effort to correlate with a known compound, **10** was submitted to ester hydrolysis (3 equiv of 1 M aqueous lithium hydroxide/methanol–tetrahydrofuran, 25 °C), acid chloride formation (10 equiv of oxalyl chloride, catalytic dimethylformamide, benzene, 25 °C, 1 h), and Barton decarboxylation (1.2 equiv of the sodium salt of 2-mercaptopyridine 1-oxide, 0.1 equiv of dimethylaminopyridine, 10 equiv of *tert*-butyl thiol, toluene reflux, 90 min)[14] to provide the bicycloundecanone **5**[15] (45% overall yield).

The ketone that was obtained was clearly different from the previously reported *cis*-bicyclo[5.3.1]undecan-11-one (**12**).[16] While the ^{13}C NMR spectrum of **12** shows the seven lines that one would expect from a compound with a plane of symmetry, the ^{13}C NMR spectrum of **5** reveals neither a plane nor an axis of symmetry. Even at 150 °C (dimethyl-d_6 sulfoxide), there was no coalescence of the 11 resonances in the ^{13}C NMR of **5**.

All attempts to interconvert **5** and **12** under either acidic or basic conditions, in an attempt to unambiguously establish the

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(13) Spectral data for **10**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.67 (s, 3 H), 3.39 (m, 1 H), 2.53 (m, 2 H), 2.39 (q, 1 H), 1.76–2.80 (m, 9 H), 1.73 (m, 1 H), 1.60 (q, 1 H), 1.49 (m, 1 H), 1.42 (m, 1 H); IR (film) 1724, 2860, 2930 cm^{-1}; MS (EI), *m/z* 224, 192, 164, 147, 136, 110, 95.

(14) Barton, D.; Crich, D.; Motherwell, W. *J. Chem. Soc., Chem. Commun.* **1983**, 939.

(15) Spectral data for **5**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.27 (m, 1 H), 2.39 (m, 1 H), 2.07 (m, 1 H), 1.08–2.00 (m, 15 H); IR (film) 1720, 2860, 2930 cm^{-1}; ^{13}C NMR (50 MHz, CDCl$_3$) 222.4, 51.2, 46.9, 34.7, 34.6, 33.4, 29.1, 28.8, 28.5, 24.2, 23.8 ppm; MS (high resolution, EI), *m/z* 166.1354 (found), 166.1357 (calcd).

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structure of **5**, were unsuccessful. Examination of molecular models reveals that the bridgehead carbon–hydrogen bonds are nearly parallel to the carbonyl group, with dihedral angles, calculated by MM2,[17,18] of 27° and 150°, so that the kinetic acidity of each is quite low.

Ketone **5** was also different from the previously reported *cis*-bicyclo[4.3.2]undecanone **14**[19] (by NMR and IR), which would have arisen from the "crossed" photoadduct **13** (Scheme III). To rule out the possibility that the product was the unknown *trans*-bicyclo[4.3.2]undecanone, an X-ray analysis was performed on the intermediate keto acid **11** (recrystallized as a monohydrate from methyl alcohol, mp 104–109 °C for the liberation of H_2O, then 137–139 °C), which confirmed the structural assignment shown for **5** (Chart I).[20] The formation of the trans isomer can be explained by a chairlike six-membered-ring transition state in the photocycloaddition. As shown in Chart I, the two bridgehead hydrogens are then necessarily trans.

In conclusion, we note that the intramolecular photocycloaddition of dioxolenones has important advantages over the more classical de Mayo diketone sequence.[21] Aside from the benefits of regiochemical control afforded by the use of the β-keto esters, this new methodology makes accessible the *trans*-bicyclo[5.3.1]undecane ring system **5**, which cannot be prepared by the standard de Mayo reaction.[22] The extension of this bicycloundecane ring construction to the synthesis of the taxanes, and the application of this methodology to the construction of other inside–outside bicycloalkanes, notably the *trans*-bicyclo[4.4.1]-undecane ring system of the ingenane diterpenes,[23] is currently under way in our laboratories.

Acknowledgment. We thank Professor Edgar Warnhoff for a generous sample of *cis*-bicyclo[5.3.1]undecan-11-one (**12**). We also thank Professors Josef Fried and Raymond Funk for valuable discussions. Support from the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Institutes of Health (CA40250 to J.D.W., GM35982 to P.G.W., and GM07148 in the form of a training grant fellowship to J.P.H.), an American Cancer Society Institutional Grant, and Merck, Sharp and Dohme is gratefully acknowledged. The NMR instruments used were funded in part by the NSF Chemical Instrumentation Program and by the NCI via the University of Chicago Cancer Research Center (CA 14599).

Supplementary Material Available: Tables of atomic coordinates, bond lengths, bond angles, anisotropic thermal parameters, and hydrogen atom positions for the crystal structure of **11** (5 pages). Ordering information is given on any current masthead page.

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(17) Calculated by using the Gajewski/Gilbert modification of the Allinger MM2 program (no. 395, Quantum Chemistry Program Exchange, Indiana University), which is commercially available through Serena Software, Bloomington, IN.

(18) Similar dihedral angles were obtained from the X-ray structure of **11**: 19° and 156°, respectively.

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(20) Data were collected on a Nicolet R3m X-ray diffractometer. All crystallographic computations were carried out using the SHELXTL programs. Lattice constants a = 6.454 (2) Å, b = 16.047 (6) Å, c = 11.752 (4) Å, and β = 99.62 (2)°, monoclinic ($P2_1/n$). R = 0.0667, R_w = 0.0883.

(21) (a) de Mayo, P. *Pure Appl. Chem.* **1964**, *9*, 597. (b) de Mayo, P. *Acc. Chem. Res.* **1971**, *4*, 41. For a recent review on the intramolecular version of this reaction, see: Oppolzer, W. *Acc. Chem. Res.* **1982**, *15*, 135.

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Photosensitization of Cobalt Bleomycin

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Received April 24, 1986

Bleomycin (Blm), a glycopeptide-derived anticancer drug,[1] causes strand scission of DNA both in vivo and in vitro.[2] Cleavage of DNA by Blm has been extensively studied, with the finding that transition-metal ions such as Fe(II) must be present.[3] Blm has also been employed in combination chemotherapy with other drugs.[4] In vitro studies have shown that the DNA-cleaving activity of Blm is substantially modified by *cis*-diamminedichloroplatinum(II); a number of new cleavage sites are produced.[5] Hence the synergism between these drugs may be related to interactions at the level of DNA drug binding.

The chemically inert complex of Blm with cobalt(III), CoBlm, is known to accumulate in certain human cancers.[6] CoBlm also binds strongly to DNA in vitro ($K_d \approx 10^{-6}$ M) and can cause DNA strand breaks when irradiated with UV light.[7] The cleavage is sequence-dependent: pyrimidines attached to the 3′-side of guanine are attacked.[7b] Presumably, cleavage of DNA is a consequence of photoreduction of CoBlm (irradiation of Co(III) complexes in the ligand-to-metal charge-transfer region often leads to production of Co(II)[8]). CoBlm does not degrade DNA when irradiated with visible light. However, the extensive studies of electron transfer from ruthenium(II) polypyridyl complexes to various cobalt(III) ammine complexes[9] suggested to us that it might be possible to use ruthenium(II) tris(bipyridyl) as a sensitizer, to activate CoBlm in the presence of visible light.

Tris(2,2′-bipyridine)ruthenium(II), $Ru(bpy)_3^{2+}$, is a small cation which is electrostatically attracted to DNA[10] and may be expected

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