racemase catalysis that made this application of the double isotope fractionation experiment possible. We are also grateful to Dr. W. W. Cleland, who has independently devised and used the double fractionation method, for communicating his work[13] prior to publication.

Registry No. Proline racemase, 9024-09-3.

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Stereoselectivity of Intramolecular Dicobalt Octacarbonyl Alkene–Alkyne Cyclizations: Short Synthesis of *dl*-Coriolin

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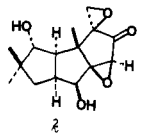
Received January 6, 1983

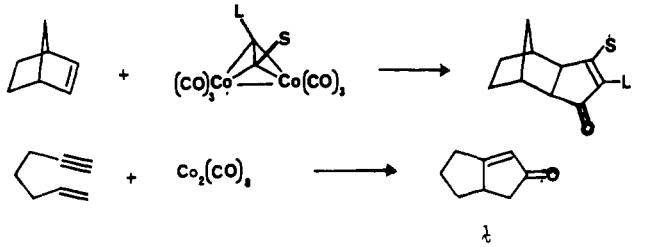
Almost a decade ago Pauson[1] reported the potentially very useful reaction of a strained alkene with an alkyne–dicobalt octacarbonyl complex, to give cyclopentenones, albeit in modest yield.[2] The cyclopentenone annulation is regiospecific; the larger group becomes adjacent to the carbonyl group. An intramolecular version of this reaction has recently been described by Schore,[3] the yield of bicyl[3.3.0]oct-2-en-3-one (**1**) was 30% (Scheme I).

If this reaction is to be of use for the synthesis of natural products, it is essential that it be stereoselective. To date there have been no studies concerned with this point. Furthermore the compatibility of this cyclization with a propargyl functionality is by no means certain.

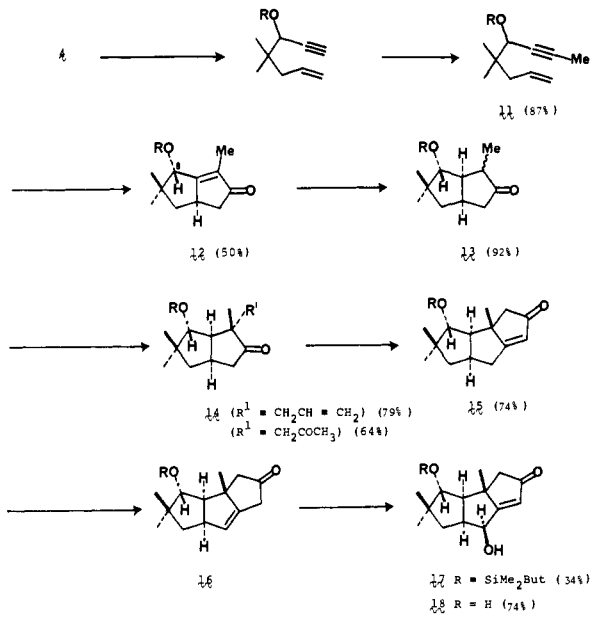
Concurrent to the above investigations, we have examined the stereoselectivity of intramolecular alkene–alkyne dicobalt octacarbonyl mediated cyclopentenone cyclizations. Here we report a stereoselective synthesis of functionalized bicyclo[3.3.0]enones and illustrate the inherent simplicity of this highly convergent methodology with a concise synthesis of the antitumor sesquiterpene coriolin **2**.[4]



Scheme I

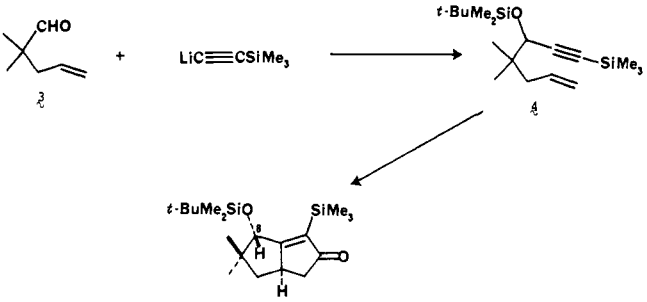


Scheme II[a]



[a] R = $SiMe_2$-*t*-Bu

Almost without exception, ring-forming processes benefit from the classical Thorpe–Ingold effect.[5] Consequently, in both conception and reality, it proved useful to exclude unsubstituted model studies. The aldehyde **3**[6] was treated with lithio(trimethylsilyl)acetylene followed by quenching by ClSi-*t*-$BuMe_2$/THF/reflux 20 h to give **4** (86%, bp 96–98 °C (0.9 mmHg)). When the enyne **4** was heated with $Co_2(CO)_8$ (1.0 equiv) in heptane (saturated with CO) at 110 °C (sealed tube), the bicyclo[3.3.0]enone **5** was isolated in 79% yield after chromatography and distillation (bp 128 °C (0.5 mmHg)), along with 3% of the C-8 epimer (26:1).



The proof of the stereochemistry depicted in **5** rests upon the following chemical and physical evidence. Hydrogenation of **5** (10% Pd/C) gave **6** (90%), which upon treatment with HBF_4/THF/H_2O gave the keto alcohol **7** (87%, mp 70.5–71.5 °C). The

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(2) Unstrained alkenes require severe conditions, and the yields of cyclopentenones are low, ca. 10–20%: Bladon, P.; Khand, I. U.; Pauson, P. L. *J. Chem. Res. Miniprint* **1977**, 0146. Khand, I. U.; Pauson, P. L. *Ibid.* **1980**, 3501; *J. Chem. Res. Synops.* **1980**, 277. For a general review of the use of organocobalt chemistry in synthesis see: Nicholas, K. M.; Nestle, M. O.; Seyferth, D. "Transition Metal Organometallics in Organic Synthesis"; Alper, H., Ed.; Academic Press: New York, 1978; Vol. II.

(3) Schore, N. E.; Croudace, M. C. *J. Org. Chem.* **1981**, *46*, 5436. Croudace, M. C.; Schore, N. E. *Ibid.* **1981**, *46*, 5357.

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(5) DeTar, D. F.; Luthra, N. P. *J. Am. Chem. Soc.* **1980**, *102*, 4505. Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 208. Eliel, E. L. "Stereochemistry of Carbon Compounds"; McGraw-Hill: New York, 1962; pp 106–202.

(6) Magnus, P.; Nobbs, M. *Synth. Commun.* **1980**, *10*, 273.

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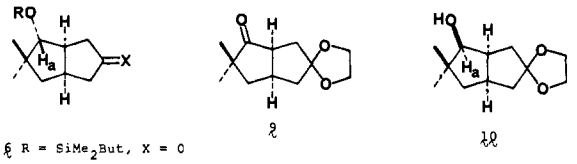

§ R = $SiMe_2But$, X = O
7 R = H, X = O
8 R = H, X = OCH_2CH_2O

derived ethylene ketal **8** (92%) on oxidation (Me_2SO/oxalyl chloride) gave **9** (67%). Reduction of **9** gave mixtures of **8** and **10** in the following ratios depending upon the reducing agent: $LiAlH_4$, 2:1; $NaBH_4$, 6:5; LiA(O-*t*-Bu)H, 2:3; Li/NH_3, 9:1. For **8** H_a, J = 7 Hz, and for **10** H_a, J = 4.5 Hz.

The reduction using Li/NH_3 is known to give the thermodynamically more stable exo-alcohol **8**, by analogy with the results obtained by Danishefsky and Ikegami,[4] in their respective syntheses of coriolin. As further proof of the syn relationship between the oxygen substituent at C-8 and C-5 hydrogen, the total synthesis of *dl*-coriolin **2** provides confirmatory evidence (Scheme II).

Treatment of **4** with $PhCH_2^+NEt_3Cl^-$/KF·$2H_2O$/THF heated at reflux (3 h), followed by *n*-BuLi/MeI/−70 to 20 °C gave **11** (87%, bp 85–90 °C (0.4 mmHg)). Exposure to **11** to $Co_2(CO)_8$/CO/heptane/110 °C/20 h in a sealed tube gave the bicyclo[3.3.0]enone **12** (50%, bp 120 °C (1 mmHg)), along with its C-8 epimer (15%, bp 130 °C (1 mmHg) 3.3:1).[7] Hydrogenation (10% Pd/C) of **12** gave **13** (92%), which was converted by standard conditions into **14** (R = allyl; 79%). Wacker oxidation of **14** (R = allyl) gave **14** (R = CH_2COCH_3; 64%), which on treatment with KO-*t*-Bu/HO-*t*-Bu at 20 °C for 0.5 h gave the tricyclic enone **15** (74%); (these last three steps were carried out in a manner similar to those described by Ikegami[4]).

Deconjugation [KO-*t*-Bu (10 equiv)/DME/20 °C/2 h, workup with AcOH][4] gave **16**, which on treatment with MCPBA (1.0 equiv)/CH_2Cl_2/1 h followed by exposure of the crude epoxide to DBU/CH_2Cl_2 gave **17** (34% from **15**). Deprotection of **17** (pyridine–polyhydrogenfluoride; according to Trost)[4] gave **18** (74%) identical with an authentic sample.

The surprise difference in stereoselectivity between the (trimethylsilyl)acetylene system **5** (26:1) and the terminal methylacetylene case **15** (3.3:1) implies that this group, which is three carbon atoms removed from both new stereocenters and itself eventually attached to a trigonal center, must exert the major influence upon the stereochemical outcome. The origin of this stereoselectivity is not known. At this stage, any speculation would not clarify the situation since the mechanism of the conversion of **4** into **5** and **11** into **12** is not well understood.

In summary, the dicobalt octacarbonyl strategy for the stereoselective synthesis of hydroxylated bicyclo[3.3.0]enones provides a short route to the tricyclic coriolin precursor **18** (12 steps, overall yield 3.2% from the readily available aldehyde **3**). Since **18** has been converted into coriolin itself, this constitutes a synthesis of the natural product and verifies the stereochemistry of the major product in the $Co_2(CO)_8$ cyclization step.

The dicobalt octacarbonyl alkene–alkyne–CO insertion reaction should provide a direct method of making many other natural and unnatural cyclopentanoid products.

Acknowledgment. The National Science Foundation is gratefully thanked for their support of this work (Grant CHE 8110674). They also provided funds (Grant CHE-8105004) for the purchase of a Nicolet 360-Hz NMR spectrometer. Professor Barry M. Trost is thanked for a comparison sample of **18** and relevant spectra.

Supplementary Material Available: NMR, melting point, and ν_{max} data for **4–9**, **11**, **12**, **14**, **15**, **17**, and **18** (3 pages). Ordering information is given on any current masthead page.

(7) All compounds were purified by chromatography over Florisil and subsequent bulb-to-bulb distillation if necessary.

Phospholipids Chiral at Phosphorus. 4. Could Membranes Be Chiral at Phosphorus?[1]

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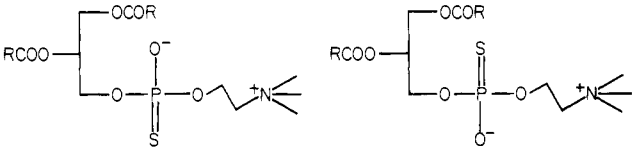
Received September 2, 1982

We present results of model study that suggest that phospholipid membranes could be chiral at phosphorus and the configuration of phosphorus could be important in the structure and properties of membranes.

The prochiral phosphorus center of phospholipids could in principle exist in four possible states in the liquid crystalline phase: (I) achiral, $^{\delta-}O\text{—}P\text{—}O^{\delta-}$; (II) chiral, O═P—$O^-$ (with the negative charge partially or fully localized); (III) chiral, $^-O\text{—}P\text{═}O$; (IV) racemic, as a mixture of II and III. This fundamental problem has never been considered in the models for membrane structures and for protein–lipid interactions, although there is increasing evidence for the involvement of the phosphate head group in protein–lipid interactions,[2] and the conformations of head group of phospholipids have been studied recently.[3]

The problem is even more intriguing when considered with the recent report of Arnett and Gold[4] that the chiral C-2 center of dipalmitoyl phosphatidylcholine (DPPC) cannot be recognized by (*R*)-*N*-(α-methylbenzyl)stearamide (NMBS), but L-DPPC is able to recognize the chiral center of NMBS. Although they provided no explanation, a very logical one is that DPPC has another chiral recognition site other than C-2. Could this be the prochiral phosphorus center?

The model compounds used for states II–IV of DPPC are the isomer A (**1**), isomer B (**2**), and mixture (A + B) (**3**), respectively



1, DPPsC (A) **2**, DPPsC (B)

(R = $C_{15}H_{31}$), of 1,2-dipalmitoyl-*sn*-glycero-3-thiophosphorylcholine (DPPsC).[5] It should be noted that in **1** and **2** the absolute configuration at phosphorus is still unknown, and the localization of the negative charge at oxygen has no experimental proof. However, on the basis of the work in the sulfur analogues of nucleotides,[6] **1** and **2** should be good models for II and III.

To compare the properties of **1–3** in the liquid crystalline phase, we chose to measure the quadrupolar splitting $\Delta\nu_Q$ in ^{14}N NMR[7] and the chemical shift anisotropy $\Delta\sigma$ in ^{31}P NMR,[8] both of which are sensitive to the structural and motional properties of the phosphate head group. Figure 1 shows the ^{14}N NMR spectra (single-pulse experiment)[9] of the unsonicated aqueous dispersion

(1) Supported by grants from NSF (PCM 8140443) and from NIH (GM30327). The NMR spectrometers used were funded by NIH GM 27431 and NSF CHE 7910019. Part 3: Bruzik, K.; Jiang, R.-T.; Tsai, M.-D. *Biochemistry*, in press. Abbreviations used: NMR, nuclear magnetic resonance; DPPC, 1,2-dipalmitoyl-*sn*-glycero-3-phosphorylcholine; DPPsC, 1,2-dipalmitoyl-*sn*-glycero-3-thiophosphorylcholine; NMBS, *N*-(α-methylbenzyl)-stearamide.

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