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INTRAMOLECULAR PHOSPHINE-DIRECTED HYDROFORMYLATION. APPLICATION TO THE TOTAL SYNTHESIS OF (+)-PHYLLANTHOCIN

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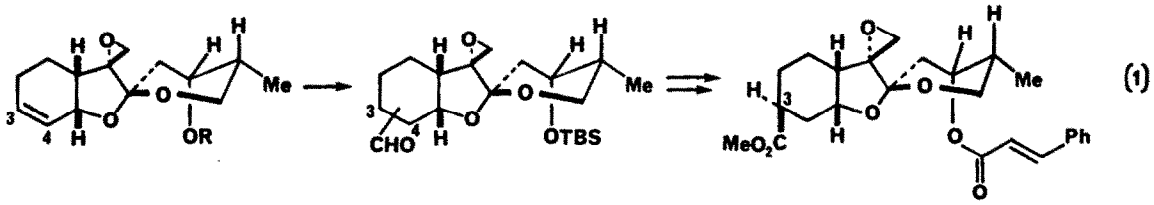
Abstract: The temporary incorporation of a coordinating phosphine residue [*m*-(Ph_2P)C_6H_4CO] into the tetracyclic phyllanthocin precursor **1a** directed the [(COD)RhOAc]$_2$-catalyzed hydroformylation of **1d** largely to the desired C(3) position. This "intramolecular hydroformylation" strategy substantially improves a key transformation in the total synthesis of (+)-phyllanthocin.

In a recent total synthesis of (+)-phyllanthocin (eq. 1),[1a] it was demonstrated that the homochiral[2] tetracyclic substance **1a**, with six of the required seven sp^3-stereogenic[3] centers introduced, was available in ten synthetic steps. However, the addition of the C(3)-methoxycarbonyl group proved to be problematic.[4] The solution, involving Rh(I)-catalyzed hydroformylation [**1b**, 1:1 CO/H_2 (560 psi), 8 mol % [(COD)RhOAc]$_2$, PhH, 76°C, 3.25 h], was not entirely satisfactory in that the mass balance was poor (53%; 21% C(3)-α-, 20% C(3)-β-, and 12% C(4)-β-formyl) and the reaction generated a multitude of uncharacterized by-products.



(1)

1a; R = H
1b; R = *t*-$BuMe_2Si$ (TBS)
1c; R = *p*-(Ph_2P)C_6H_4CO
1d; R = *m*-(Ph_2P)C_6H_4CO

Upon screening a variety of catalysts and additives[5] in attempts to improve this reaction, comparatively clean and selective production of the undesired C(4)-β-formyl regioisomer was often observed, especially with added phosphine and phosphite ligands.[6] We sought to exploit the positive features of this "phosphine effect," while overriding the tendency toward C(4)-formylation, by building the phosphine ligand into the substrate as conceptualized in eq. 2. The perceived advantages of this

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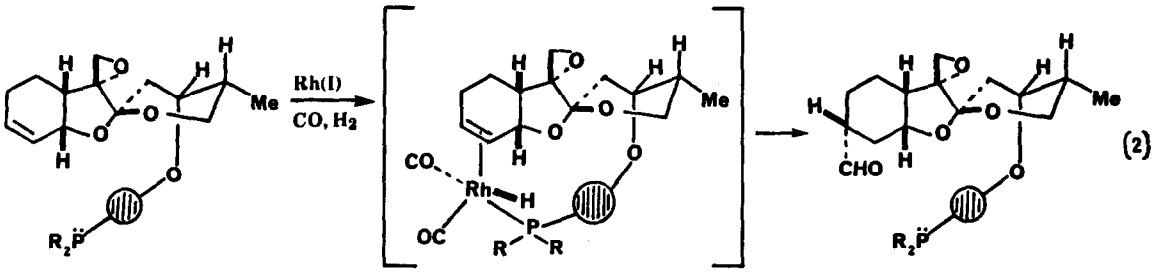
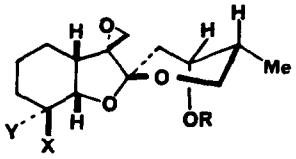
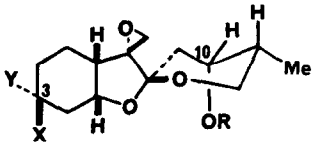
"intramolecular hydroformylation" included high effective phosphine concentration and the possibility of choosing a rigid spacer of defined length so that the C(3)-rhodium acyl intermediate would be favored.



To this end, the *para*-(diphenylphosphino)benzoate ester **1c** was prepared [**1a**, *p*-$(Ph_2P)C_6H_4CO_2H$,[7a] dicyclohexylcarbodiimide, 4-pyrrolidinopyridine, CH_2Cl_2, reflux; 77% yield][8] and subjected to hydroformylation [1:1 CO/H_2 (680 psi), 8 mol % $[(COD)RhOAc]_2$, PhH, 85°C, 3 h]. Somewhat surprisingly, starting material was recovered in 84% yield, along with a small amount (8%) of the hydroformylation/oxidation product **2b** (R=*p*-$[Ph_2P(O)]C_6H_4CO$).[9] However, subjection of the phosphine oxide derived from **1c** (30% aq H_2O_2, Et_2O, 25°C) to hydroformylation under similar conditions resulted in total consumption of the substrate and a 49% isolated yield of hydroformylation products, of which **2b** (R=*p*-$[Ph_2P(O)]C_6H_4CO$) predominated. These results suggested that the phosphine in **1c** was indeed serving as a ligand for the rhodium catalyst, but that such an association was, for the most part, shutting down the hydroformylation. We speculated that the initially chosen spacer was too long, serving to push the catalyst beyond the olefin locale. The corresponding *m*-(diphenylphosphino)benzoic acid ester **1d** was then prepared [**1a**, *m*-$(Ph_2P)C_6H_4CO_2H$,[7b] dicyclohexylcarbodiimide, 4-pyrrolidinopyridine, CH_2Cl_2, reflux; 88% yield][8] and subjected to the same hydroformylation conditions described for **1c**. The substrate **1d** was completely consumed with clean conversion to a mixture of the aldehydes **2a**, **2b**, **3a**, and **3b** (R=*m*-$(Ph_2P)C_6H_4CO$ for each) in a ratio of 1:1:7.7:0.3, measured by examination of the crude product by ^1H NMR at 400 MHz.[10] Preparatively, removal of the rhodium catalyst with bis(1,3-diphenylphosphino)propane, conversion (*t*-BuOOH, $PhCH_3$/PhH) to the phosphine oxides[9] corresponding to **2a,b** and **3a,b** and chromatography gave the latter pair in 72% yield, both useful for the production of (+)-phyllanthocin.



2a; X=H, Y=CHO
2b; X=CHO, Y=H



3a; X=H, Y=CHO
3b; X=CHO, Y=H
3c; X=CO_2Me, Y=H, R=H

The major aldehyde **3a** was epimerized (NaOH, MeOH, 25°C, 30 min) to **3b**, mp 71-73°C (73%, 18% recovered **3a**, R = *m*-[$Ph_2P(O)$]C_6H_4CO for each). Oxidation to the acid with Jones' reagent, cleavage of the C(10) ester (NaOH, MeOH, H_2O, 75°C, 30 min), and esterification (CH_2N_2, Et_2O) gave in 84% overall yield the hydroxy ester **3c**, mp 130-130.5°C, which was converted to (+)-phyllanthocin as previously described.[1a,c]

In addition to the substantial improvement of a key transformation in the synthesis of (+)-phyllanthocin,[1a] this "intramolecular hydroformylation" promises to be useful for the regio- and stereoselective addition of oxidized carbon to unactivated olefins. Systematic studies to define the scope and limitations of this process are under way.[11]

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References and Notes

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2. The term "homochiral" is used here in the sense employed by Masamune[2a] and Sharpless[2b] as a synonym for optically pure. (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (b) Behrens, C. H.; Sharpless, K. B. *Aldrichimica Acta* **1983**, *16*, 67.

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4. This strategy reflects our general interest in the functionalization, with carbon, of unactivated olefins. See: Burke, S. D.; Fobare, W. F.; Armistead, D. M. *J. Org. Chem.* **1982**, *47*, 3348.

5. Among the catalysts screened were the following: $[(COD)RhCl]_2$, $Rh_6(CO)_{16}$, Rh_2O_3, $(Ph_3P)_3RhCl$, $(CO)(Ph_3P)RhCl$, $[Rh(OAc)_2]_2$, $[(CO)_2RhCl]_2$, $[(Ph_3P)_2Rh(CO)_3]^{\oplus}ClO_4^{\ominus}$, $Co_2(CO)_8$, $Co_2(CO)_8/Ru_3(CO)_{12}$, $(Ph_3P)_3Ir(CO)H$.

6. The use of added phosphine and phosphite ligands for rate enhancement and catalyst stabilization is well-known. For general discussions of hydroformylation, see: (a) Pino, P.; Piacenti, F.; Bianchi, M. in "Organic Syntheses Via Metal Carbonyls", Wender, I.; Pino, P., Eds.; John Wiley and Sons: New York, 1977; Vol. II. (b) "Principles and Applications of Organotransition Metal Chemistry", Collman, J. P.; Hegedus, L. S.; University Science Books: Mill Valley, CA, 1980.

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9. Care must be taken to avoid extended exposure of the phosphine substrate to air, as inadvertent conversion to the phosphine oxide occurs. For product isolation, air or chemical (*t*-BuOOH) oxidation preceeded chromatography on silica gel. See: Buckler, S. A. *J. Am. Chem. Soc.* **1962**, *84*, 3093.

10. In the crude product mixture, the eight resonances due to the C(3) or C(4) methines and the associated formyl protons were distinguishable in the 400 MHz ^{1}H NMR spectrum, thus providing a reliable means of relative quantitation of the four isomeric aldehydes.

11. Conceptually related precedent for this work is available in the "remote functionalization" of the steroid nucleus by Breslow and co-workers and in the process of metal-mediated intramolecular C–H activation (cyclometalation). For key recent references, see: (a) Breslow, R.; Mehta, M P. *J. Am. Chem. Soc.* **1986**, *108*, 2485. (b) Bruno, J. W.; Smith, G. M.; Marks, T. J.; Fair, C. K.; Schultz, A. J.; Williams, J. M. *Ibid.* **1986**, *108*, 40. (c) Latesky, S. L.; McMullen, A. K.; Rothwell, I. P.; Huffman, J. C. *Ibid.* **1985**, *107*, 5981.

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