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Separation of Acetylenic Prostaglandin Isomers as Cobalt Complexes

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Summary: Previously inseparable acetylenic prostaglandins have been separated as their cobalt complexes. This methodology appears to be of broader utility.

Prostaglandins possessing a triple bond in place of the 13,14-double bond are of considerable interest since they retain the biological activities of their natural relatives.[1-9] Moreover, they are not subject to the rapid inactivation by the ubiquitous 15-hydroxyprostaglandin dehydrogenase and are inhibitors of that enzyme.[10] Diastereomers of the natural prostaglandins, e.g., 15-epimers are easily separated by chromatographic methods. Based on this finding it became possible to prepare enantiomerically pure prostaglandins by resolving, for instance, the side chain, attaching it to the racemate of the cyclopentane moiety of the molecule and separate the resulting diastereomers by chromatography. Such a strategy was successfully employed by us in the synthesis of all the classical prostaglandins,[11] as well as by others.[12] Unfortunately, this strategy could not be employed for the synthesis of acetylenic prostaglandins, since in no case, could separation of the resulting diastereomers be effected.[13] It became therefore necessary to resolve both moieties separately before attaching them to each other, requiring additional steps.

We have now discovered that the stable complexes of 13,14-dehydroprostaglandins with dicobalt octacarbonyl are readily separable by chromatography, thereby permitting the preparation of the optically pure diastereomers without resorting to a second resolution.

Since their first description by Greenfield et al.,[14] dicobalt hexacarbonyl complexes of a wide variety of acetylenes have been prepared.[15] The great stability of these complexes and the ease with which the original acetylenes can be recovered[16] suggested their use for protecting the acetylenic group during reactions with strong electrophiles[17,18] or diborane.[19]

X-Ray crystallographic and spectroscopic data indicate[15] that the complexed triple bond resembles a cis-double bond with respect to both carbon-carbon bond distance and bond angles described by the acetylenic carbons and its neighbors. This radically altered geometry, perhaps enhanced by the steric requirements of the two cobalt atoms, might be expected to influence the absorptive behavior of the complexes, thus providing a handle for the separation of diastereomeric prostaglandins.

Indeed, when the 13,14-dehydroprostaglandins 1a and 2a were converted into their

complexes with dicobalt octacarbonyl the resulting products, 3a and 4a, showed different Rf values on silica gel plates. Similarly, mixtures of 1a and 2a produced two readily separable spots. Regeneration of the prostaglandins 1a and 2a was best effected with ferric nitrate.[19] The only by-products isolated from the oxidation reaction were the two 15-ketones.[5]

The 16(S)-fluoro-13,14-dehydroprostaglandin 1b,[2,5] a very potent luteolytic agent, could not previously be prepared free from its diastereomer 2b, since resolved (3R,4S)-4-fluoro-octyn-3-ol was not available. Again, application of the above procedure effected separation. In this case repeated development of the plates and rechromatography was necessary before the pure diastereomeric cobalt complexes 3b and 4b were obtained. Also, ferric nitrate proved too slow in breaking up the cobalt complex, requiring the stronger oxidant ceric ammonium nitrate. A more satisfactory procedure for the preparation of 1b proved to be conversion of the mixture of the lactone intermediate 5 and its 15,16-epimer[5] into their easily separable cobalt complexes 6 and 7, and recovery of the individual lactone 5 and its 15(S), 16(R)-diastereomer by oxidation with ceric ammonium nitrate. The following procedures are typical:

A) Formation and Separation of Cobalt Complexes 3a and 4a. To a solution of the mixture of 13,14-dehydro-$PGF_{2\alpha}$ 1a(15 mg, 0.043 mmol) and ent-15-epi-13,14-dehydro-$PGF_{2\alpha}$ 2a (15.2 mg) in dry ether (1 ml) was added $Co_2(CO)_8$ (40 mg, 0.117 mmol). The solution was stirred at 25° under N_2 for 5 hr. Chromatography of the dried residue on four silica gel plates (Merck F-254 (0.25 mm)), with $CHCl_3/CH_3OH$/HOAc (12/0.5/0.5) yielded the cobalt complexes 3a (18.2 mg, 66%, faster moving) and 4a (18.2 mg, 66%, slower moving) after elution with ethyl acetate.

B) Oxidative Decomposition of Individual Cobalt Complexes 3a and 4a with $Fe(NO_3)_3 \cdot 9\ H_2O$. A solution of the cobalt complex of 13,14-dehydro-$PGF_{2\alpha}$ 3a (18.2 mg, 0.029 mmol) in 95% EtOH (1 ml) and $Fe(NO_3)_3.9\ H_2O$ (90 mg, 0.223 mmol) was stirred at 25° under N_2 for 4 hr. After drying (Na_2SO_4) and evaporation of the solvent, the residue was chromatographed on silica gel using dioxane/benzene/acetic acid (20/20/1). After elution with ethyl acetate 4.8 mg (48%) of 13,14-dehydro-$PGF_{2\alpha}$ (1a) was obtained. Several minor side products were observed. One of these was identified as the 15-ketone (0.8 mg, 8%). Following the same procedure, the cobalt complex 4a (18.6 mg, 0.029 mmol) yielded 4.4 mg (44%) of ent-15-epi-13,14-dehydro-$PGF_{2\alpha}$ and 0.7 mg (7%) of the 15-ketone.

C) Oxidative Decomposition of Individual Cobalt Complexes 6 and 7. To a solution of the cobalt complex 6 (17.1 mg, 0.027 mmol) in 2 ml of acetone/water (9/1) was added $(NH_4)_2 Ce(NO_4)_3)_6$ (75 mg, 0.137 mmol). After 1 min, 3 ml of water was added and the mixture extracted with ether (5 x 10 ml), dried over Na_2SO_4, and the solvent evaporated. The residue was chromatographed on silica gel (EtOAc/hexane; 4:1) yielding 7.4 mg (80%) of 15-t-butoxy-16-fluoro lactone 5. $[\alpha]_D$ = -51.9° (CH_3OH). Similarly, the cobalt complex 7 (30 mg, 0.048 mmol) furnished 14.4 mg (88%) of the 15(S)-tbutoxy-16(R)-fluoro lactone, $[\alpha]_D$ = +50° (CH_3OH).

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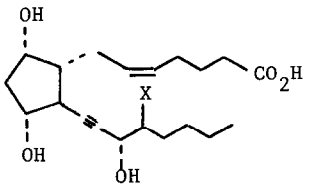
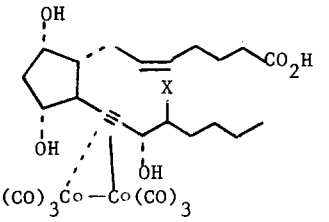


1a X=H
1b X=F

$Co_2(CO)_8$, Et_2O
$Fe(NO_3)_3 \cdot 9H_2O$, EtOH
or
$(NH_4)_2Ce(NO_3)_6$,
acetone/H_2O



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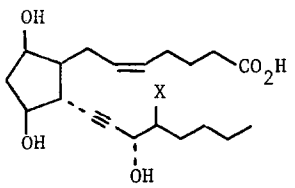
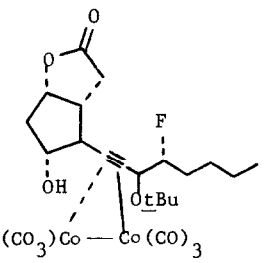
3b X=F



2a X=H
2b X=F



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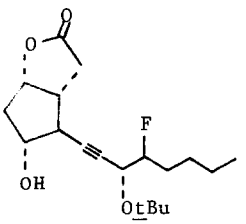

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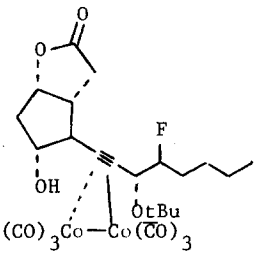
$Co_2(CO)_8$, ether
$(NH_4)_2Ce(NO_3)_6$
acetone, H_2O



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