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SYNTHESIS OF TRICARBONYLIRON COMPLEXES OF A-DI-NOR-17β-ACETOXY-1,5(10)-ESTRADIENE

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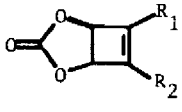
In 1970 Grubbs[1] showed that cis-3,4-carbonyldioxycyclobutenes (1) were convenient precursors of substituted tricarbonylcyclobutadieneiron complexes (2). In a later paper Grubbs and Grey[2] reported that tricarbonylcyclobutadieneiron complexes containing non-identical substituents in adjacent positions on the cyclobutadiene ring were chiral. In this paper we report a stereospecific synthesis of tricarbonyl (A-di-nor-17β-acetoxy-1,5(10)-estradiene)iron (3).



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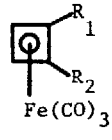

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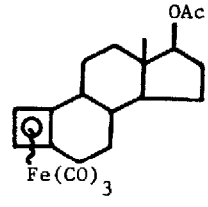
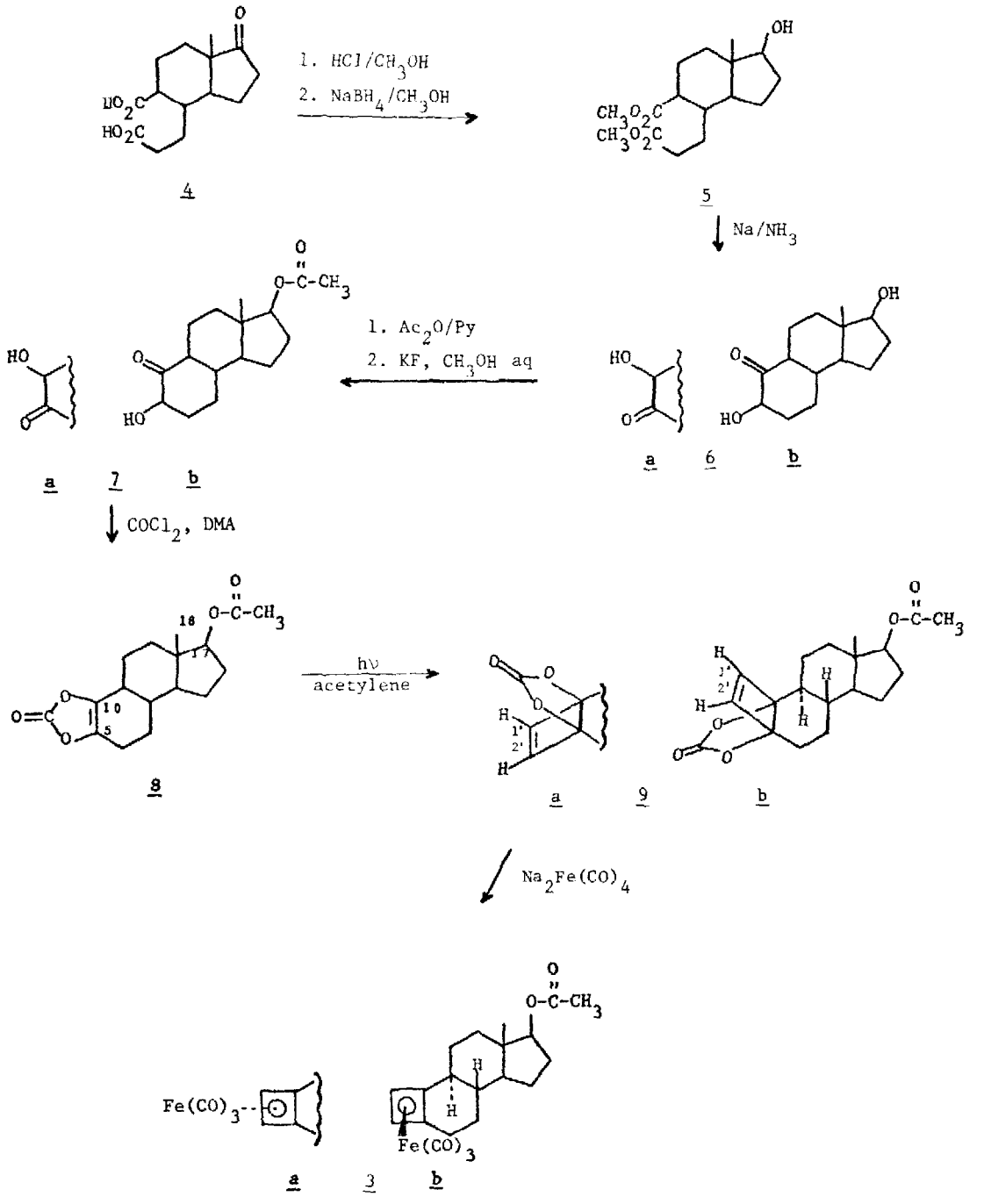


3

The synthetic route used to prepare 3 is outlined in Chart 1. Treatment of 3-(1'-oxo-8β-methyl-5β-carboxy-trans-perhydroindanyl-4α)propionic acid (4)[3] with refluxing methanolic hydrogen chloride followed by reduction with sodium borohydride in methanol at 0° gave dimethyl 3-(1'-hydroxy-8β-methyl-5β-carbomethoxy-trans-perhydroindanyl-4α)propionate (5).[4] Cyclization of 5 via the acyloin reaction gave an 82% yield of a mixture of 6a and 6b.[5]

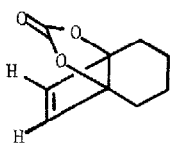
We found that acetylation of the acyloin products 6a and 6b with pyridine acetic anhydride gave a mixture of diacetates[4] which were selectively mono-deacetylated to 7a and 7b with potassium fluoride in aqueous methanol at 100°C.[6] The structure of the mono-acetates 7a and 7b were confirmed by the IR spectrum which showed hydroxyl absorption at 3490 cm^{-1} (hydroxyl α to the ketone) and the NMR spectrum which exhibited the expected downfield shift of the C_{17}–H resonance consistent with acetylation at C_{17}. In addition, the assignment of the structures of the C_{17} mono acetates was corroborated by their conversion to the vinylene carbonate acetate expected of α-ketols and described on the next page.

Chart 1


1. HCl/CH3OH
2. NaBH4/CH3OH
4
5
Na/NH3
1. Ac2O/Py
2. KF, CH3OH aq
a 7 b
a 6 b
COCl2, DMA
8
hν
acetylene
a 9 b
Na2Fe(CO)4
Fe(CO)3
Fe(CO)3
a 3 b

Treatment of mixture 7a and 7b with phosgene and N,N-dimethylaniline gave vinylene carbonate acetate 8 (75%) as a crystalline product. The vinylene carbonate 8 exhibited IR absorption at 1817 (cyclic carbonate carbonyl) and 1730 cm^{-1} (acetate carbonyl), and the nmr spectrum showed no resonance for a C_5 or C_{10} proton, thus indicating a double bond at C_5-C_{10}.

Photolysis (Rayonet photoreactor, 254 nm low pressure lamp, phenol sensitizer, 0°)[7] of an ethyl acetate solution of 8 in the presence of acetylene yielded the adducts 9a and 9b in an approximately 1:1 ratio (28% yield based on recovered 8) which were separated by chromatography on silica gel. The isomers 9a and 9b eluted had glc retention times of 8.7 and 10.3 min respectively.[8] The two isomers were distinguished by comparing the ^{13}C-NMR chemical shift of the olefinic carbons C-1' and C-2' (see structure 9) to those of the model compound 10. One of the



10

isomers of 9 showed resonances at 143.8 and 146.0 ppm for the olefinic carbons, the other isomer showed resonances at 140.8 and 148.4 ppm for the same carbons, and the model compound 10 showed a resonance at 145 ppm for the cyclobutene olefin carbons. Since C-1' and C-2' of both 9a and 9b are subject to the same number of α- and β-effects,[9,10] any difference in chemical shifts would be due to long range interactions. Examination of molecular models of 9a, 9b and 10 showed that the olefinic carbons of 9a and 10 are subject to similar substituent effects and would be expected to show similar chemical shifts. In addition, C-1' of 9b is subject to the most γ interactions and would be expected to show the most upfield resonance for the carbon in question. Based on the foregoing analysis, we have assigned structure 9b to the isomer possessing the 140.8 and 148.4 ppm resonance and structure 9a to the other isomer.

When 9a or 9b was treated separately with disodium tetracarbonylferrate under conditions similar to those used by Grubbs[11] to prepare simple cyclobutadieneiron tricarbonyls, different isomers of tricarbonyl(A-di-nor-17β-acetoxy-1,5(10)-estradiene)iron complexes (3) were obtained.[12] The mass spectrum of both isomers showed a parent ion at m/e 412 and fragment ions for successive losses of CO at 384, 356 and 328 m/e expected for cyclobutadiene iron tricarbon complexes.[13] The nmr spectra of vicinally substituted, unsymmetrical cyclobutadiene iron tricarbonyl complexes show two singlets for the olefinic protons with no observable spin-spin coupling.[14] Therefore, both 3a and 3b would be expected to exhibit two singlets for the cyclobutadienyl protons. The ^{1}H-NMR spectrum of the steroid cyclobutadiene product from 9a exhibit singlets at δ 3.90 and 3.76 ppm, and the product obtained from isomer 9b showed singlets at δ 4.10 and 3.74 ppm for the cyclobutadienyl protons.

Although the ^{1}H and ^{13}C-NMR spectra of 3a and 3b are different, we have been unable to confidently establish the correct stereochemistry of the two products. However, the fact that 9a and 9b gave different steroid tricarbonylcyclobutadieneiron isomers showed for the first ti

that this reaction was stereospecific, and the isolation of only one isomer from each reaction supported the observations of Grubbs and co-workers[2] that optically active tricarbonylcyclobutadiene iron complexes are relatively resistant to racemization.

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References and Notes

1. R. H. Grubbs, J. Amer. Chem. Soc., 92, 6693 (1970).

2. R. H. Grubbs and R. A. Grey, Chem. Comm., 76 (1973).

3. D. M. Piatak, G. Herbst, J. Wicha and E. Caspi, J. Org. Chem., 34, 116 (1969).

4. All new compounds showed satisfactory IR, ^{1}H- and ^{13}C-NMR, and ms data. Compounds 6, 7a, 7b, 8, 9a and 9b gave satisfactory analytical data. Compounds 3a and 3b decompose slowly at room temperature and were not submitted for elemental analysis.

5. J. C. Sheehan, R. A. Coderre and P. A. Cruickshank, J. Amer. Chem. Soc., 75, 6231 (1953).

6. Protection of the C-17 hydroxyl group was necessary to prevent side reactions during the phosgenation step.

7. The conditions for this reaction were developed from model studies on the photosensitized cycloaddition of acetylene to dimethylvinylene carbonate and tetramethylenevinylene carbonate. Ethyl acetate (100 ml) as solvent containing 298 mg 8 and 5 g phenol was employe

8. Gas-liquid chromatographic analyses were carried out using a Varian Model 1400 instrument equipped with a 3' column packed with 2% SE-30 on Chromosorb W. The oven temperature was 220°C.

9. G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N. Y., 1972.

10. J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N. Y., 1972.

11. R. H. Grubbs, personal communication.

12. When an approximately 1:4 mixture of 9a and 9b was treated with disodium tetracarbonylferrate·dioxonate (Alfa Products-Ventron), a 26% yield (based on recovered 9b) of 3a and 3b was obtained. The reaction yields are variable and further dependent on the ratio of 9a:9b as 9b generally gives a lower yield of tricarbonyliron complex than does 9a.

13. R. G. Amiet, P. C. Reeves and R. Pettit, Chem. Comm., 1208 (1967).

14. G. Berens, F. Kaplan, R. A. Rimerman, B. W. Roberts and A. Wissner, J. Amer. Chem. Soc., 97, 7076 (1975), and references therein.