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Resolution and absolute configuration of dimethyl hydroxy-(ferrocenylmethyl)phosphonate

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Abstract—Racemic dimethyl hydroxy-(ferrocenylmethyl)phosphonate *rac*-**1** was resolved via the formation of diastereomeric esters with (*S*)-α-methoxy-α-phenylacetic acid. The diastereomers, separated by column chromatography, were stereospecifically hydrolyzed by dissolution in trifluoroacetic acid at −30 °C and quenching with water. The absolute configuration of one enantiomer of **1** was assigned by X-ray diffraction.

1. Introduction

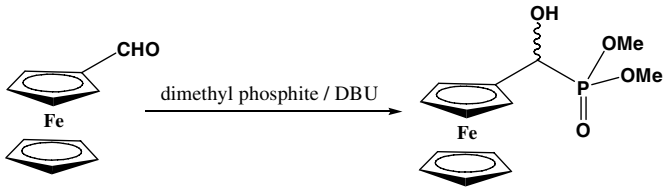
The introduction of ferrocenyl groups into biologically active molecules can result in novel, unexpected features of bioconjugates.[1] For example, the replacement of the phenyl group in the anti-breast cancer drug, tamoxifen, by the ferrocenyl moiety resulted in a broader spectrum of biological activity.[2] Another aspect stimulating the research of ferrocenyl conjugates of biologically active molecules is their redox activity, enabling the development of electrochemical methods which can detect these molecules in biological samples.[3]

α-Hydroxyphosphonates and the corresponding phosphonic acid display a wide spectrum of biological activity.[4] A variety of routes to enantiomerically pure compounds have been developed via either enantioselective synthesis[5] or resolution of racemates.[4,6] We thought that it would be of interest to develop a route to enantiomerically pure (or at least enantiomerically enriched) ferrocenyl α-hydroxyphosphonates with the purpose of studying their biological activity and to use them in stereoselective syntheses of other functionalized ferrocenyl phosphonates (e.g., aminophosphonates) and phosphonic acids.

Racemic ferrocenyl[7]- and (1,1′-diphosphaferrocenyl)[8] α-hydroxyphosphonates are readily available via the addition of dialkyl phosphites to the corresponding metallocene aldehydes. Herein, we report the resolution of racemic dimethyl hydroxy-(ferrocenylmethyl)phosphonate *rac*-**1** via the formation of diastereostereomeric esters with (*S*)-α-methoxy-α-phenylacetic acid (*S*)-MPA. The absolute configuration of one enantiomer of **1** was determined by X-ray diffraction.

2. Results and discussion

Racemic **1** is available by the addition of dimethylphosphite to ferrocenecarboxaldehyde.[7] We have slightly modified the original procedure by using DBU in place of triethylamine, which resulted in a better yield of **1** (85% compared with 68%) and significantly shorter reaction time (overnight compared with 10–12 days).



rac-**1**

The treatment of *rac*-**1** with (*S*)-MPA, DCC and DMAP afforded a mixture of diastereomeric esters (*R*,*S*)-**2** and (*S*,*S*)-**2**, easily separable by column chromatography

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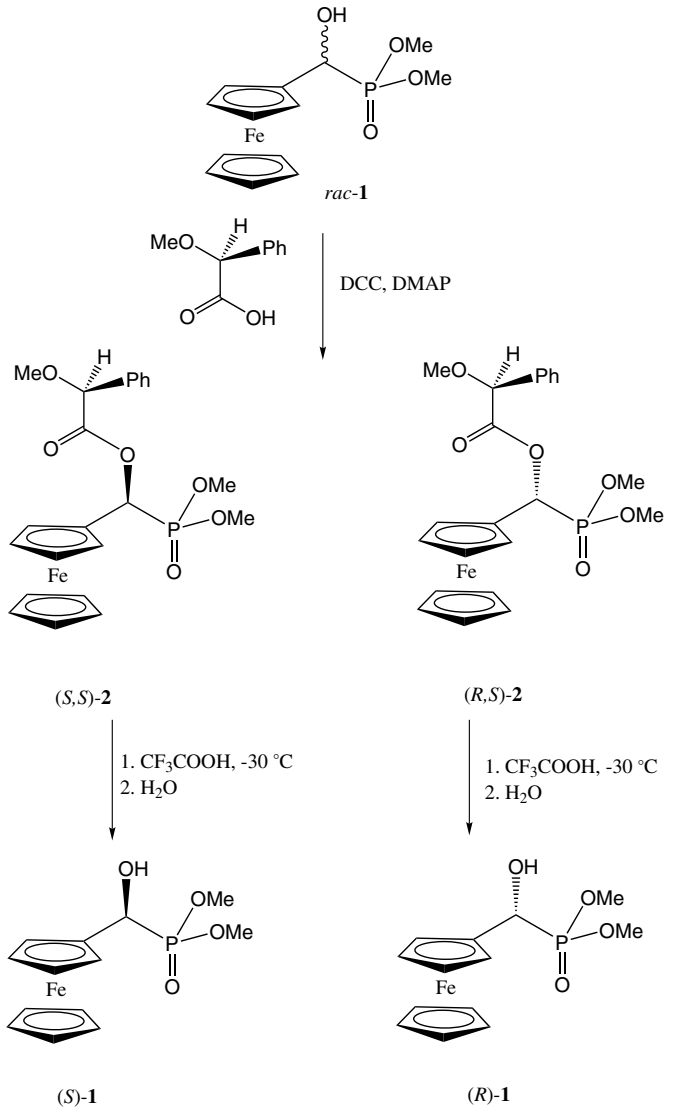
(Scheme 1). We assigned their absolute configuration using ^{1}H and ^{31}P NMR spectra. The spectra show a significant shielding of one methoxy group in the less polar diastereomer and of the ferrocenyl moiety in its more polar counterpart. Furthermore, the ^{31}P NMR signal of the less polar diastereomer appears at a higher field than that of its more polar counterpart. Using a generally accepted model of the preferred conformation of MPA esters,[9] one can assign the (*R*,*S*)- and (*S*,*S*)-configuration for the less polar and the more polar stereoisomer, respectively (Fig. 1).



Scheme 1. DMAP = 4-(dimethylamino)pyridine; DCC = *N*,*N*′-dicyclohexylcarbodiimide.

Having separated (*R*,*S*)-**2** and (*S*,*S*)-**2**, we attempted to hydrolyze them in order to obtain both enantiomeric forms of **1**. Unfortunately, our first attempts failed, resulting in the recovery of ferrocenecarboxaldehyde or racemic **1** when the hydrolysis was carried out in an aqueous alkaline or acidic solutions, respectively [racemization was confirmed by ^{1}H NMR of the sample derivatized with (*S*)-MPA as described above]. However, we found that

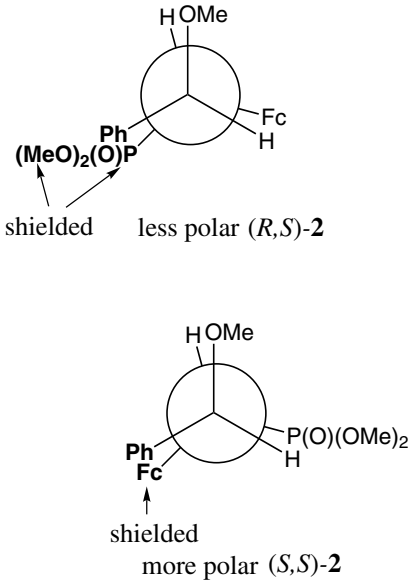


Figure 1. Extended Newmann projections of the preferred sp conformations[9] of (*R*,*S*)-**2** and (*S*,*S*)-**2**.

by dissolving the diastereomers in trifluoroacetic acid at −30 °C and subsequent quenching with water afforded the enantiomers of **1** in good yields (85–90%) and 94% ee (Scheme 1). This suggests that under these conditions, a typical retentive S_N1 reaction,[10] involving a configurationally stable ferrocenylcarbenium ion, took place. However, slight racemization was observed, which indicates that rotation around the bond linking Cα with the Cp ring in the carbenium ion is possible to some extent. Recrystallization of the samples from dichloromethane–hexane did not improve the ee.

Direct evidence for the retention of configuration in this reaction was provided by the X-ray structure of the enantiomer of **1** obtained from the less polar diastereomer (*R*,*S*)-**2**. A crystal of this enantiomer suitable for X-ray analysis was obtained from layered dichloromethane–hexane solution. The molecular structure is shown in Figure 2.

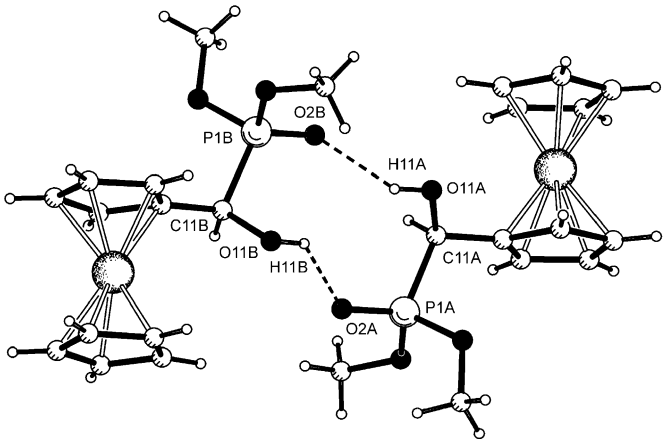


Figure 2. The molecular structure of (*R*)-**1** showing cyclic hydrogen-bonded dimers.

The structure reveals an (*R*)-configuration at the stereogenic Cα centre, in keeping with the configuration of the starting mandelate assigned by NMR, and retention of configuration during hydrolysis. Similarly as with other α-hydroxyphosphonates, (*R*)-**1** forms in solid state noncentrosymmetric hydrogen-bonded dimers.

3. Conclusion

In conclusion, we have elaborated upon an efficient way to synthesize both enantiomers of **1** (94% ee), and determined their absolute configurations.

4. Experimental

All reactions were carried out under argon. The solvents were freshly distilled over appropriate drying reagents. For flash chromatography, silica gel 60 (Merck, 230–400 mesh ASTM) was used. All reagents were purchased from Aldrich and were used without further purification. NMR spectra were registered on a Varian Gemini 200 BB spectrometer (200 MHz for ^{1}H) in $CDCl_3$ solutions using internal TMS (for ^{1}H) and external 85% H_3PO_4 (for ^{31}P) references. IR spectra were recorded on a FT-IR Nexus Nicolet apparatus. Optical rotations were taken on a Perkin–Elmer 241 polarimeter in a 1 dm tube. Elemental analysis was performed by Analytical Services of the Centre of Molecular and Macromolecular Studies of the Polish Academy of Sciences (Łódź).

4.1. Synthesis of *rac*-1

A mixture of ferrocenecarboxaldehyde (214 mg, 10 mmol), dimethyl phosphite (110 mg, 10 mmol) and DBU (50 μl) was stirred overnight at rt and then subjected to flash chromatography (eluent: ethyl acetate). *rac*-**1** was obtained as a yellow solid. Yield 275 mg (85%). Mp 109–111 °C (lit. mp 103–105 °C).[7] ^{1}H NMR: δ 4.59 (dd, $J = 4.6$, 8.5 Hz, 1H, Cα–H), (4.41 bs, 2H, Cp), 4.32 (bs, 2H, Cp), 4.25 (s, 5H, Cp′), 2.79 (dd, $J = 4.6$, 14.4 Hz, disappears after addition of D_2O, OH). ^{31}P NMR: δ 22.40. IR (KBr, cm^{-1}): 3328, 1230, 1074, 1050, 1031. Anal. calcd for $C_{13}H_{17}FeO_4P$: C, 48.18; H, 5.29. Found: C, 48.24; H, 5.29.

4.2. Synthesis of (*R*,*S*)-2 and (*S*,*S*)-2

To a solution of *rac*-**1** (324 mg, 1 mmol), (*S*)-MPA (249 mg, 1.5 mmol) and 4-(dimethylamino)pyridine (25 mg, 0.25 mmol) in dichloromethane (5 ml), DCC (0.5 M solution in dichloromethane, 3 ml, 1.5 mmol) was added and the resulting mixture stirred overnight at rt. The solid formed was filtered off, and the filtrate evaporated to dryness. Column chromatography (eluent: ethyl acetate–dichloromethane 1.5:1) afforded two fractions: less polar containing (*R*,*S*)-**2** and more polar containing (*S*,*S*)-**2**.

(*R*,*S*)-**2**: (175 mg, 37%). ^{1}H NMR: δ 7.56 (m, 2H, Ph), 7.39 (m, 3H, Ph), 6.17 (d, $J = 10.7$ Hz, 1H, *CH*-P), 4.94 (s, 1H, *CH*-OMe), 4.38 (m, 1H, Cp), 4.15–4.25 (m, 3H, Cp), 4.03 (s, 5H, Cp′), 3.52 (s, 3H, C–O*Me*), 3.50 (d, $J = 10.8$ Hz, 3H, P–O*Me*), 3.37 (d, $J = 10.8$ Hz, 3H, P–O*Me*). HRMS (EI) calcd for $C_{22}H_{25}FeO_6P$ 472.07382, found 472. 07371. ^{31}P NMR: δ 17.25.

(*S*,*S*)-**2**: (165 mg, 35%). ^{1}H NMR: δ 7.60 (m, 2H, Ph), 7.43 (m, 3H, Ph), 6.20 (d, $J = 10.4$ Hz, 1H, *CH*-P), 4.96 (s, 1H, *CH*–OMe), 4.31 (m, 1H, Cp), 4.13 (m, 1H, Cp), 4.06 (m, 1H, Cp), 3.93 (m, 1H, Cp), 3.73 (s, 5H, Cp′), 3.68 (d, $J = 10.8$ Hz, 3H, P–O*Me*), 3.61 (d, $J = 10.8$ Hz, 3H, P–O*Me*), 3.49 (s, 3H, C–O*Me*). HRMS (EI) calcd for $C_{22}H_{25}FeO_6P$ 472.07382, found 472.07411. ^{31}P NMR: δ 17.53.

4.3. Hydrolysis of (*R*,*S*)-2 and (*S*,*S*)-2

The ester (156 mg, 0.33 mmol) was dissolved in CF_3COOH (5 ml) at −30 °C and the resulting solution was stirred at this temperature for 10 min. Quenching with water (50 ml), extraction with dichloromethane and column chromatography (eluent: ethyl acetate) afforded (*R*)-**1** {$[\alpha]_D^{18} = -97$ (*c* 0.3, $CHCl_3$)} and (*S*)-**1** {$[\alpha]_D^{18} = +97$ (*c* 0.3, $CHCl_3$)} in 85–90% yield. ^{1}H and ^{31}P NMR spectra of these compounds were identical with those of *rac*-**1**.

4.4. Crystallographic data

Crystallographic data (excluding structure factors) for (*R*)-**1** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 608067. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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