mg), which were identified as aryl vinyl sulfide 2 by spectral data: mp 200–201 °C (hexane–benzene); ^{1}H NMR (CCl_4) δ 2.23 (s, Me, 3 H), 6.25–7.33 (m, ArH, 24 H); ^{13}C NMR ($CDCl_3$) δ 15.29, 121.63, 125.24, 126.64, 126.91, 127.34, 127.50, 127.80, 128.11, 128.30, 128.52, 129.40, 129.47, 130.21, 130.45, 130.70, 131.37, 132.71, 135.73, 136.14, 137.41, 138.30, 140.82, 142.32, 143.45, 143.73, 143.77, 147.01; MS (*m/z*, rel intensity) 668 (M^+ + 2, 13), 666 (M^+, 11), 587 (M^+ – Br, 27), 301 ($Ph_2C{=}C^+C_6H_4SMe$, 100), 254 (301 – MeS, 41). Anal. Calcd for $C_{40}H_{31}BrS_2$: C, 73.75; H, 4.68. Found: C, 73.45; H, 4.57.

Photolysis of Arylvinyl Bromides 1 with Methyl Phenyl Sulfide. A solution of arylvinyl bromide 1 (2 mmol) in acetonitrile (100 mL) was irradiated in the presence of methyl phenyl sulfide (10 mmol) by use of a Pyrex-filtered Hg lamp (100 W) at 10 °C for 3–4 h under a nitrogen atmosphere. After removal of the solvent and excess methyl phenyl sulfide, crystalline phenyl vinyl sulfide 4 was filtered and washed with hexane. Additional sulfide 4 was obtained from the mother liquor by column chromatography on silica gel with dichloromethane–hexane eluent. The results and spectral data of the products are given in Table I. In the photolysis of arylvinyl bromide **1b**, 4-methoxy-1-(phenylthio)-9-phenylphenanthrene was isolated by column chromatography on silica gel from the product mixture: mp 119–121 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.97 (s, OMe, 3 H), 6.93–8.71 (m, ArH, 17 H); MS (*m/z*, rel intensity) 392 (M^+, 100). Picrate: mp 144–146 °C (EtOH). Anal. Calcd for $C_{33}H_{23}O_8N_3S$ (picrate): C, 63.76; H, 3.73; N, 6.76. Found: C, 64.17; H, 3.75; N, 6.85.

Investigations Utilizing the ^{18}O Isotope Shift in ^{13}C Nuclear Magnetic Resonance Spectroscopy. 2. Observation of a Downfield Isotope Shift in 2,6-Dimethyl-4-pyrone[1]

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Introduction

The effects of isotopic substitution on the chemical shift of various NMR-active nuclei have been an area of research for a number of years. With a few exceptions, heavy isotopic substitution induces upfield chemical shifts in NMR spectra.[2-4] Oxygen-18-induced isotope shifts have been reported for a number of nuclei; substitution of ^{18}O for ^{16}O has thus far been reported to induce an upfield isotopic shift on NMR signals.[5] Properties for the ^{18}O isotope shift in ^{13}C NMR spectroscopy have been studied extensively, and this phenomenon has found application as a primary technique in different kinds of experimental problems.[5] In this paper, we report the first observation of a *downfield* ^{18}O isotope shift in the ^{13}C NMR spectrum of 2,6-dimethyl-4-pyrone (2,6-dimethyl-4*H*-pyran-4-one (1; Figure 1)). There are two oxygen atoms in this aromatic, heterocyclic compound: a carbonyl oxygen and a ring oxygen. Upon substitution of the ^{16}O carbonyl oxygen for ^{18}O, the ^{18}O isotope shift of the C-4 carbonyl carbon was 33 ppb (parts per billion) upfield, and the three-bond ^{18}O isotope shift of the C-2 ring carbon was 9 ppb *downfield*. The isotope shifts were used to follow simultaneously by ^{13}C NMR an acid-catalyzed oxygen exchange reaction of the carbonyl oxygen.

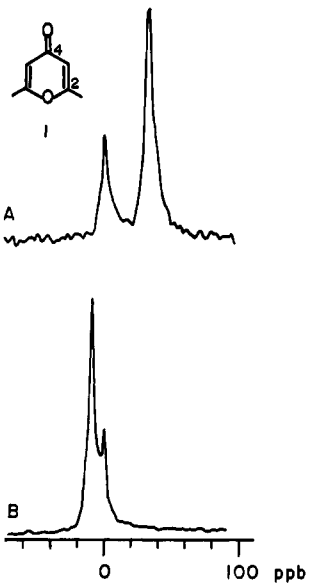

Figure 1. ^{13}C NMR signals (A) for the C-4 carbonyl carbon and (B) for the C-2 ring carbon in [4-^{18}O]-2,6-dimethyl-4-pyrone. A 1 M solution of 2,6-dimethyl-4-pyrone in 80% [^{18}O]water was incubated at pH 1.09, 70 °C for 40 h, and the ^{13}C NMR spectrum was recorded at 75.5 MHz. The sample contained 70% ^{18}O. The chemical shift for each carbon in the unlabeled (^{16}O) isotopomer has a value of 0 ppb, and upfield shifts are positive.[5] A one-bond upfield ^{18}O isotope shift of 33 ppb is observed for the C-4 carbon and a three-bond *downfield* ^{18}O isotope shift of 9 ppb is observed for the C-2 carbon. Unlabeled 2,6-dimethyl-4-pyrone was added to this sample to verify this interpretation of the ^{13}C NMR data.

Experimental Section

2,6-Dimethyl-4-pyrone was purchased from Aldrich and was used without further purification. [^{18}O]Water (97 atom % ^{18}O) was purchased from Merck and [^{2}H]water (99.9 atom % ^{2}H) from Aldrich. All other reagents were either analytical or spectrometric grade.

NMR Spectra. Natural abundance ^{13}C NMR spectra were recorded at 75.5 MHz at ambient temperature (1400-Hz sweep width, 66° pulse angle, and a 16K data block). Protons were broad-band decoupled. The accumulated FID was zero-filled one time before a line-broadening factor was applied. The error in the measured isotope effect was ±1 ppb.

Measurement of the ^{18}O Isotope Shifts. A 1 M solution of 2,6-dimethyl-4-pyrone was prepared in 80% [^{18}O]water, 10% [^{2}H]water at pH 1.09 and incubated at 70 °C for 40 h. Mass spectral analysis on a DuPont 21-490 mass spectrometer showed incorporation of one ^{18}O atom. The ^{18}O isotope shifts were determined by recording three ^{13}C NMR spectra. First, the ^{13}C NMR spectrum of ^{18}O-labeled 2,6-dimethyl-4-pyrone was recorded. A quantity of unlabeled 2,6-dimethyl-4-pyrone was added to the sample to give a 1.5 M solution of the compound, and the ^{13}C NMR spectrum was recorded. An additional quantity of unlabeled 2,6-dimethyl-4-pyrone was added to the sample to give a 2.0 M solution of the compound, and the ^{13}C NMR spectrum was recorded.

Kinetics of Oxygen Exchange. Oxygen exchange reactions were followed by measuring the rates of incorporation of ^{18}O from the solvent $H_2{}^{18}O$ as described.[6] The solutions for the exchange reactions were prepared in 5-mm NMR tubes by dissolving 2,6-dimethyl-4-pyrone in 0.5 mL of buffered solutions of 80% [^{18}O]water, 10% [^{2}H]water at the required pH (e.g., 5 mM KCl/HCl at pH 1.09); the final concentration of 2,6-dimethyl-4-pyrone was 2 M. The solution was equilibrated in a water bath

(1) (a) Part 1: Risley, J. M. *Magn. Reson. Chem.* **1991**, *29*, 143–147. (b) This work was supported in part by funds from the Foundation of The University of North Carolina at Charlotte and from the State of North Carolina. (c) We thank Prof. Lou Daignault for his assistance with the mass spectrometric analysis.

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at the desired temperature. A discontinuous assay mode was used to follow the oxygen exchange reactions.[6] In this procedure, the NMR tube containing the reaction solution was removed from the water bath at varying intervals, rapidly cooled in a 5 °C water bath to room temperature for acquisition of the ^{13}C NMR spectrum, and subsequently returned to the temperature bath for further incubation. The area under each peak was measured using peak heights and a deconvolution routine, and the relative concentration of each isotopic species present was calculated.[6,7] (Mega[7] has shown quite convincingly that peak height measurements can be used to quantitate accurately relative concentrations of isotopomers in solution.) The pseudo-first-order rate constants were calculated as previously described.[6]

Discussion

Measurement of the ^{18}O Isotope Shifts. After incubation at pH 1.09, 70 °C in 80% [^{18}O]water, the ^{13}C NMR spectrum of a 1 M solution of [^{18}O]-2,6-dimethyl-4-pyrone (70 atom % ^{18}O) was recorded at 75.5 MHz. Figure 1A shows the ^{13}C NMR signal for the C-4 carbonyl carbon, and Figure 1B shows the ^{13}C NMR signal for the C-2 ring carbon; the two signals in Figure 1A are separated by 33 ppb and in Figure 1B by 9 ppb. Mass spectral analysis of ^{18}O-labeled 2,6-dimethyl-4-pyrone indicated the incorporation of one ^{18}O, and yet the ^{13}C NMR signals of the C-4 and C-2 carbon atoms each showed two signals in a ratio of 70:30, but reversed (Figure 1). These apparently contradictory results were resolved upon addition of unlabeled compound to the ^{18}O-labeled sample. Upon additions of two portions of unlabeled 2,6-dimethyl-4-pyrone to ^{18}O-labeled 2,6-dimethyl-4-pyrone, the intensity of the downfield ^{13}C NMR signal of the C-4 carbonyl carbon (Figure 1A) increased as the percentage of ^{18}O in the sample decreased from 70% ^{18}O to 47% ^{18}O to 35% ^{18}O. Thus, the ^{13}C NMR signal of the C-4 carbonyl carbon in 2,6-dimethyl-4-pyrone is shifted upfield upon isotopic substitution with ^{18}O, as expected.[5] The magnitude of the isotope shift is 33 ppb. This is a much smaller isotope shift than would typically be expected for a ketone, which generally has an isotope shift of ~50 ppb[5] and is also smaller than would be predicted on the basis of the ^{17}O NMR chemical shift[1a] for the carbonyl oxygen in 4-pyrone.[8] But this reflects a diminished double-bond character of the carbonyl group due to the aromatic character of this heterocyclic compound as coincidentally the isotope shift (33 ppb) falls intermediate between cyclohexanone (52.2 ppb) and phenol (16 ppb).[5]

However, upon addition of unlabeled 2,6-dimethyl-4-pyrone to ^{18}O-labeled 2,6-dimethyl-4-pyrone, the intensity of the upfield ^{13}C NMR signal of the C-2 ring carbon (Figure 1B) increased as the percentage of ^{18}O in the sample decreased from 70% ^{18}O to 47% ^{18}O to 35% ^{18}O. This is a totally unexpected result and indicates that the ^{13}C NMR signal for the C-2 ring carbon in 2,6-dimethyl-4-pyrone is shifted *downfield* upon isotopic substitution with ^{18}O. This is the first observation of a downfield ^{18}O isotope shift in ^{13}C NMR spectroscopy, and, indeed, the first observation of a downfield ^{18}O isotope shift for any NMR-active nucleus.[5] Although downfield isotope shifts upon heavy isotopic substitution are unusual occurrences in NMR spectroscopy, a number of downfield isotope shifts have been observed, most of which are ^{2}H isotope effects over two to four bonds; however, downfield ^{2}H isotope effects over one bond and over five to seven bonds have also been detected.[3,4] Although rare, the downfield ^{18}O isotope shift in ^{13}C NMR is not unprecedented, but this observation strongly suggests that caution is needed to ascertain whether an upfield or a downfield ^{18}O isotope effect is being exerted on an NMR signal. These results indicate that the incorporation of ^{18}O occurred only in the carbonyl group and not in the ring to give [4-^{18}O]-2,6-dimethyl-4-pyrone; the isotope shift on the C-2 carbon is a three-bond downfield effect. Previously, a three-bond upfield ^{18}O isotope effect had been observed in dimethylmaleic anhydride.[7]

There is further supporting evidence for this analysis of the ^{13}C NMR spectra. First, different natural products possess a basic 4-pyrone structure. The ^{18}O isotope shift in ^{13}C NMR has been used to study the source (origin) of oxygen atoms in the biosynthesis of natural products,[5] among which are diplosporin (a 4-pyrone derivative)[9,10] and four xanthone (dibenzo-4-pyrone, 2) derivatives: sterigmatocystin,[11-13] ravenelin and ravenelin triacetate,[14] shamixanthone,[15] and tajixanthone.[15] The upfield ^{18}O isotope shifts for the carbonyl (C-4 or C-9) carbon in these natural products were as follows: diplosporin, 35 ppb; sterigmatocystin, 29 and 32 ppb; ravenelin, 27 ppb; ravenelin triacetate, 37 ppb; and tajixanthone, 27 ppb. The ^{18}O isotope shift for the C-4 carbon in 2,6-dimethyl-4-pyrone (33 ppb) is in general agreement with these observations. On the other hand, only in the xanthone derivatives were the one-bond ^{18}O isotope shifts for the 4a and 10a carbons reported, and all as upfield shifts: sterigmatocystin, 21 ppb; ravenelin, 19 ppb; ravenelin triacetate, 21 ppb; shamixanthone, 23 and 25 ppb; and tajixanthone, 23 and 24 ppb. The ^{18}O isotope shift for the C-2 carbon in 2,6-dimethyl-4-pyrone (9 ppb downfield) is, of course, in considerable disagreement with these observations. Furthermore, while one-bond downfield ^{18}O isotope shifts in ^{13}C NMR could be anticipated on the basis of an empirical relationship observed between ^{18}O isotope shifts and ^{17}O NMR chemical shifts,[1a] it would not be expected in this compound on the basis of ^{17}O NMR chemical shifts for the O-1 oxygens in 4-pyrone derivatives.[8] Finally, the magnitudes of the ^{18}O isotope shifts for the 4a and 10a carbons in the natural products are more easily interpreted with the present observation of a three-bond downfield isotope effect. Other oxygen heterocyclic, aromatic compounds such as furans and pyrylium have shown large upfield ^{18}O isotope shifts of ~40 ppb.[5] In unsaturated ethers, much smaller ^{18}O isotope shifts of ~17 ppb are observed.[5] An aromatic character of 2,6-dimethyl-4-pyrone that is intermediate between these for the C-2 carbon (analogous to the C-4 carbon (in the previous text)) might be expected to result in an upfield ^{18}O isotope shift of ~30 ppb for the

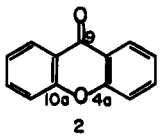

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Table I. Pseudo-First-Order Rate Constants for the Oxygen Exchange Reaction of the Carbonyl Oxygen in 2,6-Dimethyl-4-pyrone

pH	temp, °C	pseudo-first-order rate constant, k (s^{-1}) × 10^7
1.09	30.0	4.69 (3.95)[a]
	60.0	59.5 (54)
	70.0	147 (140)
	80.0	425 (417)
3.24	30.0	<21.7
	80.0	<17.5
5.54	30.0	<12.4
7.01	30.0	<8.82
9.04	30.0	<8.77

[a] Values are calculated from the data for the C-4 carbonyl carbon. Values in parentheses are calculated from the data for the C-2 ring carbon.

C-2 carbon; this is a value anticipated on the basis of ^{17}O NMR chemical shifts[18] for O-1 oxygens in 4-pyrone derivatives.[8] Because ^{18}O isotope shifts are generally additive,[5] the sum of the expected upfield isotope shift (30 ppb) and a three-bond downfield isotope effect (−9 ppb) yields an upfield isotope shift of ~21 ppb—a value in general agreement with the isotope shifts reported in the natural products.

Kinetics of Oxygen Exchange. 2,6-Dimethyl-4-pyrone was dissolved in a buffered solution containing 80% [^{18}O]water and 10% [^2H]water, and the incorporation of ^{18}O from the solvent into the compound was followed by ^{13}C NMR spectroscopy in a discontinuous assay mode. The small volumes of the solutions (0.5 mL) used permitted rapid equilibration (no more than ~2 min) of the 5-mm NMR tubes both at elevated temperatures and at ambient temperature prior to acquisition of the ^{13}C NMR spectra during the exchange reactions. Accurate records were kept of the times the solutions were maintained at the elevated temperatures during each exchange reaction to assure an accurate calculation of pseudo-first-order rate constants; the short times required for the sample to equilibrate at each step in the analysis had no affect on the values for the rate constants. During the period the solution was at ambient temperature for acquisition of the ^{13}C NMR spectra, the exchange reactions were undetectable. At pH 3.24, 5.54, 7.01, and 9.04 at 30 °C and at pH 3.24 at 80 °C no oxygen exchange reactions at either the carbonyl carbon or the ring carbon were detected over a period of as long as 37 days and therefore the values for the pseudo-first-order rate constants listed in Table I are upper estimates with the actual values being much less.

A typical set of ^{13}C NMR spectra for an acid-catalyzed oxygen exchange reaction at pH 1.09, 70 °C is shown in Figure 2. Figure 2A shows the exchange reaction for the C-4 carbonyl carbon. As the exchange reaction proceeds, the ^{13}C NMR signal for the ^{18}O-labeled carbonyl group appears 33 ppb upfield and increases in intensity. Figure 2B shows the same reaction for the C-2 ring carbon. As the exchange reaction proceeds, the ^{13}C NMR signal of the ring carbon appears 9 ppb downfield and increases in intensity. Thus, under these conditions, ^{18}O incorporation occurs only in the carbonyl group, and no oxygen exchange was detected for the ring oxygen. The ^{18}O isotope shifts of both the C-4 carbonyl carbon and the C-2 ring carbon were used to follow simultaneously the oxygen exchange reaction of the carbonyl oxygen. Pseudo-first-order rate constants were calculated from both sets of data. These values at different temperatures are given in Table I; the standard deviation in k is ±5%. The values for the pseudo-first-order rate constants at pH 1.09 are, within experimental error, identical whether the one-bond upfield isotope shift is used or the three-bond downfield isotope shift is used. The energy of activation for the acid-catalyzed oxygen exchange reaction of the carbonyl oxygen at pH 1.09 is 17 kcal/mol.

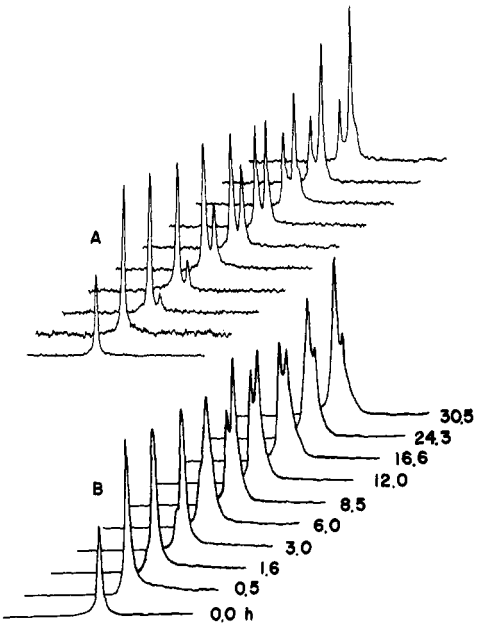

Figure 2. Typical acid-catalyzed oxygen exchange reaction of the carbonyl oxygen in 2,6-dimethyl-4-pyrone at pH 1.09, 70 °C. The sample contained 2 M pyrone in 80% [^{18}O]water, 10% [^2H]water and 5 mM KCl/HCl buffer to maintain pH. The spectra were recorded at the times indicated in the figure. (A) ^{13}C NMR signal for the C-4 carbonyl carbon. As the reaction proceeds, the intensity of the upfield ^{13}C NMR signal increases with exchange of ^{18}O from the solvent. (B) ^{13}C NMR signal for the C-2 ring carbon. The intensity of the downfield ^{13}C NMR signal increases upon incorporation of ^{18}O from the solvent into the carbonyl group as the exchange reaction approaches equilibrium.

There have been few studies of the oxygen exchange reactions of heterocyclic oxygen compounds. One study reported quantitative data for the 2,4,6-trimethylpyrylium cation.[16] The majority of the studies reported qualitative analyses of the incorporation of ^{18}O into 4-pyrone and some 4-pyrone derivatives upon incubation in acidic, neutral, or basic media.[17-22] Beak and Carls[17] reported that upon incubation of 2,6-dimethyl-4-pyrone (and 3,5-dimethyl-4-pyrone) in 6.55% [^{18}O]water at pH 2.75 for 26 h at 98 °C less than 2% ^{18}O incorporation was detected by mass spectral analysis, whereas under the same conditions both oxygens in 4-pyrone were exchanged and had reached equilibrium. They concluded "[t]he failure of [2,6-dimethyl-4-pyrone], which might reasonably be expected to incorporate the label, to do so is presumably simply a reflection of the lower reactivities of these compounds under the reaction conditions".[17] Our results are consistent with this conclusion. After 450 h at pH 3.24 at 80 °C, the ^{13}C NMR spectrum showed no detectable oxygen exchange

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reaction at either the carbonyl carbon or the C-2 ring carbon.

Ichimoto et al.[19] did not study 2,6-dimethyl-4-pyrone but did report the results for oxygen exchange reactions in 4-pyrone and some 4-pyrone derivatives, primarily in alkali solutions of 1.5% [^{18}O]water at 40 °C for 20 h; mass spectrometry was used to analyze the results. At pH 1.0 and at "neutral" pH under the same conditions, 4-pyrone and kojic acid were reported to have incorporated ^{18}O at about one-fifth the value detected in basic solution. They concluded from their studies that "...the ^{18}O incorporation in the ring oxygen is larger than that in the carbonyl oxygen" in acidic, neutral, or basic solution. They also concluded that substitution of a methyl group on the 2- and 6-positions of the heterocyclic ring reduces the rate at which oxygen exchange occurs in the ring. They proposed that an electron-releasing group such as a methyl group suppresses nucleophilic attack at the C-2 and C-6 positions and thus reduces the rate of ring opening for an exchange reaction to occur. From their data it is not possible to assign a number to the magnitude of the rate reduction effected by methyl group substitution. Our results for 2,6-dimethyl-4-pyrone show that at pH 1.09 the only oxygen exchange reaction detected is for the carbonyl oxygen.

The order of magnitude of the rate for the oxygen exchange reaction of the carbonyl oxygen in 2,6-dimethyl-4-pyrone is consistent with data for these reactions in carbonyl groups: cyclopropenones,[23] acetone,[24,25] cyclohexanone,[25] acetophenones,[23,26] and benzophenones.[27] The energy of activation for the carbonyl oxygen exchange reaction of benzophenones in acidic aqueous dioxane is ~19 kcal/mol,[27] which is very similar to the value we obtained for 2,6-dimethyl-4-pyrone. Mechanisms for oxygen exchange reactions in 4-pyrones were proposed by Beak and Carls[17] and by Ichimoto et al.[19] According to these mechanisms, ^{18}O exchange at the carbonyl group occurs upon attack by [^{18}O]water in acidic solution at the C-4 carbon. Our results are in agreement with these proposals.

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Practical Synthesis of an Enantiomerically Pure Synthon for the Preparation of Mevinic Acid Analogues

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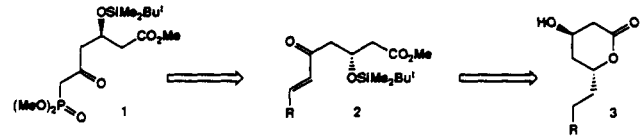
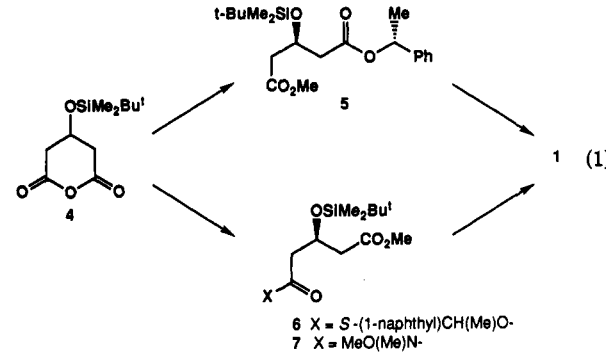
Heathcock and co-workers[1] have elegantly demonstrated the utility of the optically active β-keto phosphonate 1 in their synthesis of compactin and its analogues. This synthon allows for the direct introduction, via a Horner-Emmons condensation, of a highly functionalized side chain suitable for conversion into the 3-hydroxypyranone moiety (e.g., 3) found in the mevinic acid family of HMG-CoA reductase inhibitors and their synthetic analogues.[2]



Heathcock has reported[1,3] two routes to β-keto phosphonate 1 that rely on the highly diastereoselective reaction of prochiral anhydride 4[4] with either (*R*)-1-phenylethanol or (*S*)-1-(1′-naphthyl)ethanol for the introduction of asymmetry (88–95% diastereomeric excess). For the conversion of 5 to 1, it was necessary to desilylate 5 prior to reaction with dimethyl (lithiomethyl)phosphonate to prevent β-elimination of the (*tert*-butyldimethylsilyl)oxy group. Similarly, the condensation of 7 with dimethyl (lithiomethyl)phosphonate is extremely sensitive to reaction conditions due to a competitive retro-aldol reaction and β-elimination of the silyloxy group. Diesters 5 and 6 were converted to β-keto phosphonate 1 in overall yields of 34 and 59%, respectively.



Although this chemistry has been used to prepare 1 in multigram quantities, the cost and availability of the required 1-arylethanols in enantiomerically pure form limit its preparative utility. In this paper, we report an alternative synthesis of 1 that utilizes commerically available (*S*)-1-phenethylamine as the source of chirality and can be used for the large-scale preparation of 1 (Scheme I).

Reaction of anhydride 4 with (*S*)-1-phenethylamine in the presence of triethylamine with toluene as solvent (−78 °C, 4.5 h) gave a 79:21 mixture of diastereomeric acids 8a

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(4) Rosen, T.; Watanabe, M.; Heathcock, C. H. *J. Org. Chem.* **1984**, *49*, 3657. Anhydride 4 is now commerically available from the Aldrich Chemical Co.

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