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An Intramolecular Silyl Transfer from the Carboxylate to the Hydroxyl Group in Sodium 4-Hydroxybutyrate and Its Application to the Synthesis of Injectable Antifungal Posaconazole Derivative, Sch 59884

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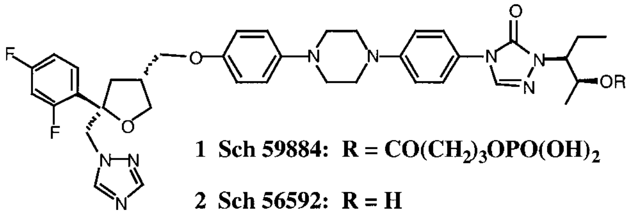
Abstract:

Discovery of a novel intramolecular silyl group migration from a carboxylic acid to the hydroxyl group of sodium 4-hydroxybutyric acid, unraveling of its reaction mechanism and application of this finding to the synthesis of injectable antifungal Sch 59884 are described.

Recently, we described a synthesis of the injectable antifungal Sch 59884, **1**, from posaconazole (Sch 56592), **2**, via the *p*-nitrobenzoate ester of 4-hydroxybutyric acid.[1] Although this synthesis was scaled up to prepare several kilograms of the antifugal, the *p*-nitrobenzyl was far from a desirable protecting group. Not only did it involve the use of the irritant *p*-nitrobenzyl halide, but its deprotection with either Na_2S or Zn/HCl was also problematic. The sulfide method required rigorous emission controls and led to decomposition of intermediates, whereas the zinc method formed polymeric byproducts which entrained the intermediates, making their isolation difficult which lowered yields upon scale-up.



1 Sch 59884: R = CO(CH$_2$)$_3$OPO(OH)$_2$

2 Sch 56592: R = H

To overcome the above difficulties alternate synthetic strategies were proposed. In one of our strategies we envisaged transient protection of the carboxylic group of commercially available sodium 4-hydroxybutyric acid, **3**, which may then be *O*-phosphorylated at the hydroxyl moiety. For phosphorylation DBCP (dibenzylchlorophosphate) appeared to be the reagent of choice as conditions for the synthesis of the resultant intermediates (**6**, **7**) as well as for the deprotection of the benzyl group were well-characterized and were high-yielding. This made efficient use of multichiral-centered and expensive **2**.[2] Protection of the carboxylic acid function with silyl-protecting reagents appeared attractive because after the phosphorylation of the alcohol moiety the silyl group could be removed under mild conditions, preferably during the reaction workup. This strategy is outlined in Scheme 1. For the conversion of **3** to its silyl-protected derivative **4**, readily available TBDMS-Cl was used first.[3]

Compound **3** is insoluble in solvents such as THF, *t*-BuOMe; hence, DMF (or DMSO) was chosen for the reaction of **3** with TBDMS-Cl. Even in these solvents **3** was sparingly soluble, and the reaction remained heterogeneous from the beginning to the end (due to formation of NaCl as the byproduct). Initially the reaction of a slight excess of **3** with TBDMS-Cl was conducted at room temperature for an overnight period. After an aqueous extractive workup, compound **8a** was isolated instead of **4a**![4] Lowering the reaction temperature and/or time did not favor the formation of **4a** over **8a**. This was intriguing, unanticipated, and for the above synthetic strategy undesirable. We decided to probe this reaction with the hope that the results could be made more favorable once the causes for the undesirable outcome were identified. Since there is no chromophore in the reactants, and since **4a** could be labile to the moisture on TLC plates, a noninvasive analytical method was desirable. Hence, the above experiments were conducted in d_7-DMF (or d_6-DMSO) so that they could be monitored in real time via NMR.[5]

A NMR study[6] for the reaction of **3** with TBDMS-Cl showed the following: typically the silylation reactions (Scheme 2) started with two new sets of proton signals (compared to those for **3**), one major and one minor. With time, the decrease in the major set of signals reciprocated an increase in the other set of proton signals (the latter were

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(1) Lee, G. M.; Gala, D.; Eckert, J.; Schwartz, M.; Renton, P.; Pergamen, E.; Whttington, M.; Schumacher, D.; Heimark, L.; Shipkova, P. Synthesis of Injectable Antifungal Sch 59884. *Org. Process Res. Dev.* **2000**, *5*, 622−629.

(2) Andrews, D. R.; Gala, D.; Gosteli, J.; Gunter, F.; Mergelsberg, I.; Sudhakar, A. Process for the Preparation of Triazolones. U.S. Patent 5,625,064, April 29, 1997.

(3) Although TMS-Cl is readily available and less expensive than TBDMS-Cl, the former was expected to be unstable as a carboxylic acid-protecting group, especially in view of the fact that both silylation as well as phosphorylation generated HCl as a byproduct. Hence, TMS was not considered as a viable silyl-protecting reagent.

(4) A slight excess of **3** was used in these reactions to ensure nonacidic conditions throughout the reaction and workup and to minimize the chance of disilylation of **3**. Aqueous extractive work up in *t*-BuOMe allowed for the removal of excess of **3**, and subsequent brine wash removed most of the DMF from the product.

(5) ^{1}H NMR signals for various intermediates were expected to be more informative for understanding this reaction compared to the data obtained via in situ monitoring with IR spectroscopy.

(6) Standard condition for the NMR studies of silyl transfer in deuterated solvents: **3** (1.0 mmol) was mixed with d_6-DMSO or d_7-DMF (2 mL) at room temperature under N_2 atmosphere, and appropriate silyl chloride (0.95 mmol) was added dropwise. The reaction mixture was analyzed by NMR (the sample was prepared by mixing 0.5 mL of the reaction mixture with 0.5 mL of either d_6-DMSO or d_7-DMF).

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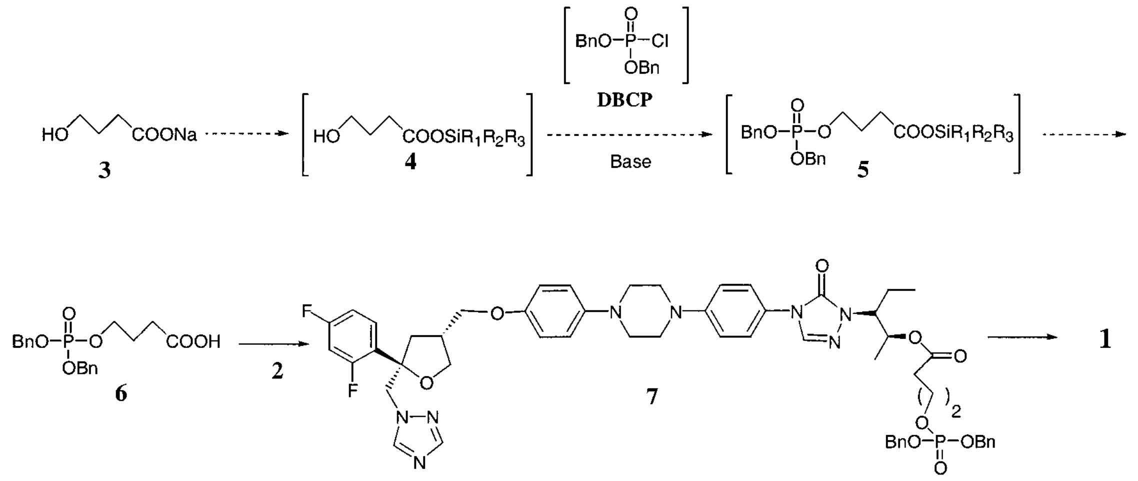
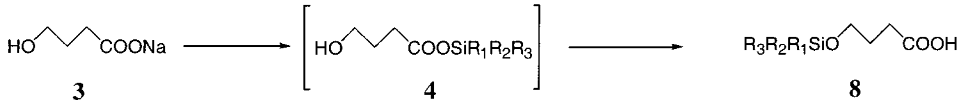
Scheme 1: **Proposed route to 1 via carboxysilyl 4**



Scheme 2: **Silylation of sodium 4-hydroxybutyrate 3**



a: $R_1=R_2=$ Me, $R_3=$ *t*-Bu
b: $R_1=R_2=$ Ph, $R_3=$ *t*-Bu
c: $R_1=R_2=R_3=$ *i*-Pr

shown in isolated **8a**). On this basis, it was hypothesized that initial silylation of **3** occurred at the carboxylate moiety, forming **4a**. Then the silyl group, under the reaction conditions, migrated to the hydroxyl group in an intramolecular fashion to form **8a**. In both solvents (DMF and DMSO) changing the concentration of reactants did not alter the ratio of **4a** to **8a** or the high yield[7] of product. Finally, limiting the silylating reagent to 0.5 mol equiv also led to both set of protons with the similar changes in the pattern described above without the formation of γ-lactone as judged by NMR. If this were an intermolecular silyl-transfer reaction, two other products would be expected: (i) varying amounts of the bis-silylated **3** (and hence a third set of proton signals) and (ii) γ-lactone (via a spontaneous irreversible cyclization of 4-hydroxybutyric acid which would inevitably form in an intermolecular silyl-transfer reaction). Neither one of these compounds was detected by ^{1}H NMR.[8] Both of these observations remained true for the alternate silylating reagents described later in this manuscript, and supported the above intramolecular silyl-transfer hypothesis.

Table 1. **Silylation of 3 with various silyl chlorides in d_7-DMF**

reaction conditions	product ratio by NMR[a]
TBDMS-Cl, rt, 0.5 h	**4a**:**8a**::85:15[b]
TBDMS-Cl, rt, 20 h	**4a**:**8a**::20:80
TBDPS-Cl, rt, 0.5 h	**4b**:**8b**::85:15
TBDPS-Cl, rt, 20 h	**4b**:**8b**::5:95[b]
TRIPS-Cl, rt, 0.5 h	**4c**:**8c**::80:20
TRIPS-Cl, rt, 20 h	**4c**:**8c**::30:70

[a] Sparing solubility of **3** in DMF leads to only a trace of NMR signal for **3**; hence, the extent of reaction cannot be determined by NMR. [b] Compounds **4a** and **4b** were unstable to aqueous workup; however**, 8a** and **8b** were isolated in 80% yield.

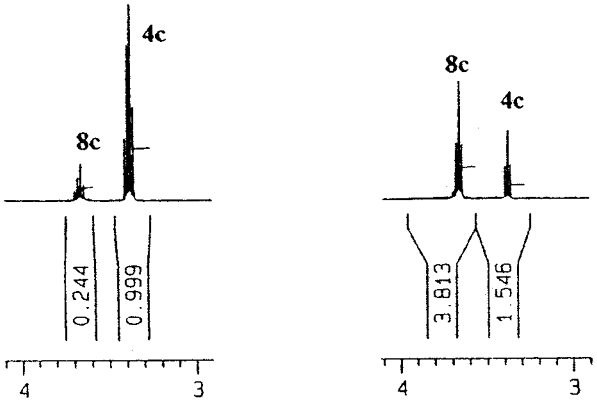


Figure 1. **Chemical shifts of $\underline{CH_2}OH$ in 4c and $-\underline{CH_2}OSiR_3$ in 8c. Silylation of 3 with TRIPSCl in d_7-DMF after 0.5 h and 20 h (3−4 ppm spectra are shown).**

Bulky silyl groups should slow the migration and allow for the synthesis of **4**. To this end *tert*-butyldiphenylsilyl chloride (TBDPS-Cl) and triisopropylsilyl chloride (TRIPS-Cl) were evaluated. The results of this study are summarized in Table 1. In both cases the formation of both the hydroxy- and the carboxy-silylated products were seen at the inception of the reactions. The use of more reactive TRIPS-triflate in place of TRIPS-Cl also generated the mixture of products. Apparently the reaction of the former reagent with **3** was not fast enough to overcome the silyl migration and allow for the clean formation of **4c**. With the TRIPS group, the silyl migration was slower compared to that for the TBDMS group, and the intermediates **4c** and **8c** were stable which

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(7) After workup 70−85% isolated yield for 4-*O*-silylated butyric acids was realized. DMF carried some product in the aqueous layer during the workup.

(8) Varian and Bruker 400 MHz NMR were used for this study. Control experiments suggested that the high sensitivity of these instruments could have detected about 1% (mol) of γ-lactone in the reaction mixture.

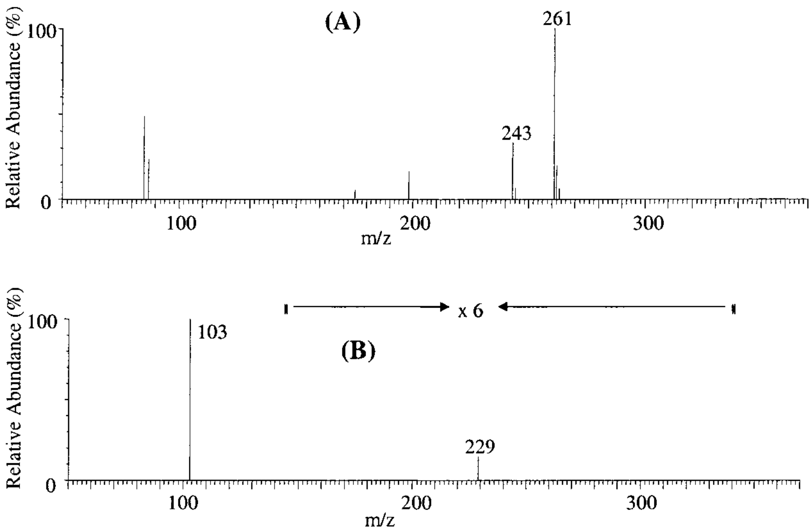

Figure 2. **Mass spectra data for 4c.**

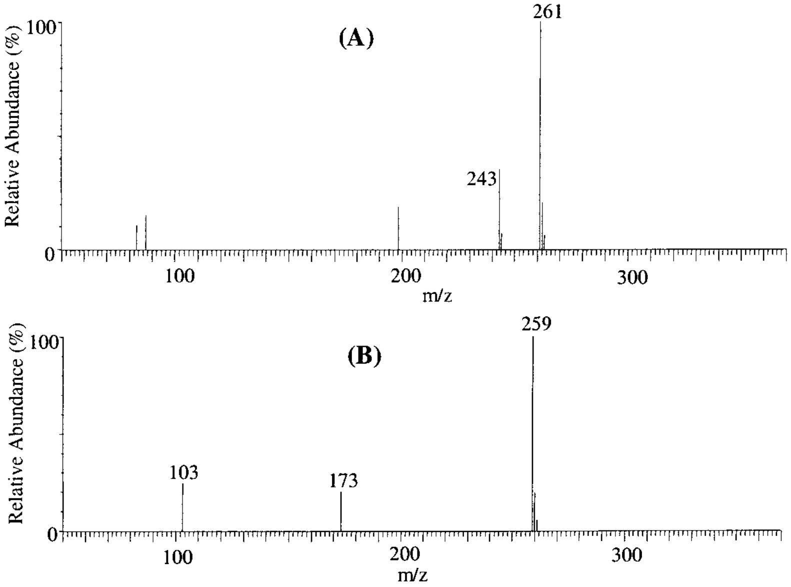

Figure 3. **Mass spectra data for 8c.**

allowed for their isolation. The process of silyl transfer in **3** with TRIPS-Cl as observed by NMR as well an unequivocal identification of the isolated compounds **4c** and **8c** via electrospray ionization mass spectrometry (ESI-MS) are depicted in Figures 1−3. These studies confirmed the structures of the *O*-silyl butyrates **4c** and **8c**, and hence support the silyl migration in general for **3**.

As shown in Figure 1, the reaction of **3** and $^{i}Pr_{3}SiCl$ started with two new sets of proton signals, at 3.4 ppm for **4c** ($-C\underline{H}_2OH$) and 3.7 ppm for ($-C\underline{H}_2OSi^{i}Pr_3$) **8c**. With time the decrease of the signal at 3.4 ppm reciprocated the increase in proton signal at 3.7 ppm. After mild acid/base aqueous workup, these signals remained in the respective isolated products.

The structures of **4c** and **8c** were differentiated by negative-ion ESI-MS studies**.** Figure 2 illustrates both the positive-ion ESI-MS spectrum (Figure 2A) and negative-ion ESI-MS spectrum (Figure 2B). For compound **4c**, the positive-ion ESI-MS displayed a protonated molecular ion at *m*/*z* 261 (Figure 2A), while no deprotonated molecular ions ($[M - H]^- = 259$) were observed for **4c** in the negative-ion mode (Figure 2B), indicating the absence of the −COOH group in the molecule. The protonated molecular ion $[M + H]^+$ at *m*/*z* 261 shown in Figure 3A indicated a molecular mass of 260 Da for **8c**. The presence of deprotonated molecular ion $[M - H]^-$ at *m*/*z* 259 in Figure 3B is strong evidence for the acidic structure **8c**.

Thus, even with the TRIPS group the synthesis of pure **4c** was not likely. At this stage we revised our synthetic strategy to accommodate this facile silyl transfer, which did not add steps to the synthesis of **1** (Scheme 3). TBDMS-Cl[9] was chosen as the silylating reagent due to its (i) ease of migration, (ii) reagent cost, (iii) the stability of **8a** to aqueous workup conditions, (iv) the stability of **8a** to the reaction conditions during coupling with **2** (the mixed anhydride

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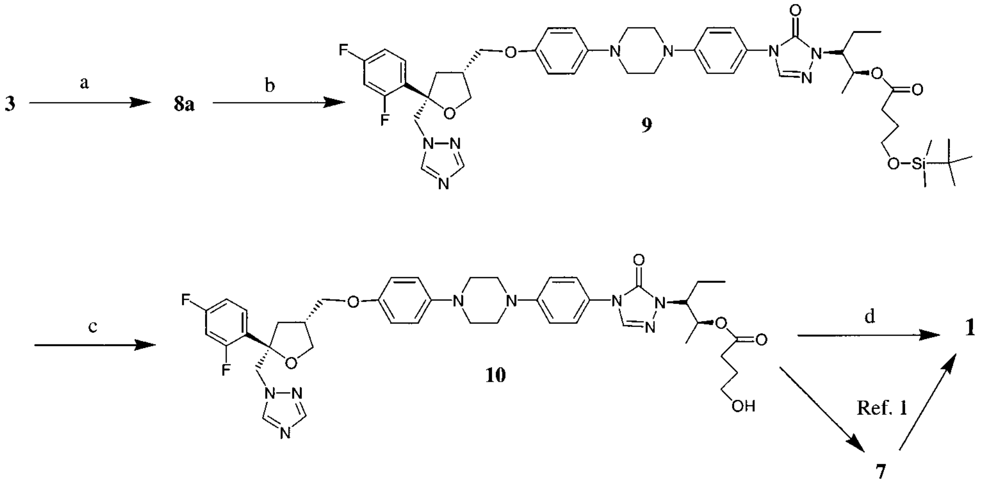
(9) Of the three silylating reagents evaluated, TBDMS was the most cost-effective reagent; hence, it was chosen. The use of trimethylsilyl (TMS) was minimally explored. TMS appeared more labile than TBDMS during the isolation of 4-hydroxy-TMS-butyrate. The use of TMS group was expected to require more stringent reaction and workup conditions due to its aqueous and thermal instability.

Scheme 3: **Revised synthesis of 1**[a]



[a] a) 1 equiv TBDMS-Cl, DMF, rt, 3−4 h; 80%. b) **2**, TsCl, DMAP, THF, 0 °C to rt, 24 h; 98%. c) 5% aq HCl, THF, 0 °C to rt, 4 h; 87%. d) i) $POCl_3$, THF, −30 °C; ii) aq $NaHCO_3$, rt, 18 h; 77%.

approach), and (v) the subsequent facile removal under dilute acid conditions to minimize hydrolysis of **9** and **10**. Hence, intermediate **8a** was used for the preparation of **1**. First the synthesis and isolation of **8a** were optimized to obtain 80% isolated yield of **8a**.[7] Coupling of **8a** with **2** to produce **9** progressed well using the mixed anhydride conditions[1,2] in near quantitative isolated yield without any noticeable desilylation of **8a** or **9** (HPLC).

The conversion of **9** to **1** proved challenging and required a major effort. Solubilities of the compounds in this series were such that only THF or CH_2Cl_2 could be used for practical purposes, but the latter was excluded for environmental reasons. Due to its water miscibility, the isolation of product required considerable care. Desilylation of **9** with TBAF resulted in the formation of large amounts of **2**.[10] The use of buffered conditions (TBAF/glacial CH_3COOH)[11] lowered the amount of **2** but caused some acylation of **10** to form **11** which could not be purged through the rest of the synthesis. On this basis, mineral acids were evaluated for the conversion of **9** to **10**. Here aqueous sulfuric acid, aqueous phosphoric acid, and aqueous hydrochloric acid led to a varying degree of desilylation. Optimization led to the use of hydrochloric acid for an efficient (complete desilylation, 87% isolated yield with some loss to the aqueous layers) conversion of **9** to **10**. Compound **10** is a solid, but it can be converted without isolation to form **1** if needed. Coupling of **10** with DBCP (dibenzylchlorophosphate) progressed slowly to the previously known intermediate **7**, which has been deprotected under transfer hydrogenation conditions to the injectable antifungal **1**.[1]

The reaction of **10** with freshly prepared DBCP under the previously described conditions showed that this reaction was very slow. At the end of 24 h about 20% of **10** was converted to **7** compared to complete reaction in a few hours at 0 °C for the previous substrate.[1] It was recognized that the presence of a primary alcohol group in **10** in the revised synthesis presented an opportunity to avoid the use of unstable DBCP, thereby eliminating the preparation and storage of hazardous DBCP. Of several phosphorylating reagents evaluated (e.g., pyrophosphoric acid, polyphosphoric acid, diphenylchlorophosphate, tetrachloropyrophosphate) the readily available, inexpensive $POCl_3$ was eventually selected as the reagent of choice.

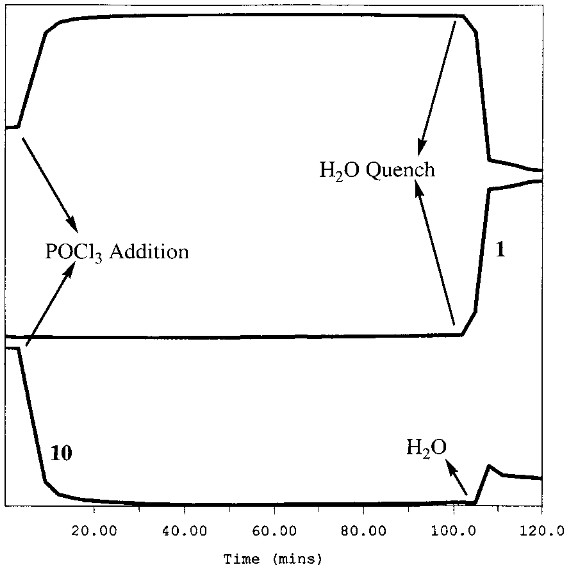


Figure 4. **Conversion of 10 to 1: Concirt ReactIR profile. [Concirt and ReactIR are registered trademarks of Mettler-Toledo Inc.].**

Since HPLC monitoring of the phosphorylation reaction requires quenching of reaction samples, which is a slow reaction and generates impurities as described later in this manuscript, an alternative real-time monitoring technique was desirable. In this regard, in situ infrared spectroscopy via the use of ReactIR was useful in monitoring the disappearance of **10**, and the formation of **1**. As shown in Figure 4, the reaction of **10** with $POCl_3$ at −5 to 0 °C was complete within minutes after the addition of $POCl_3$ (consumption of **10**, the lowest line complemented by the formation of the

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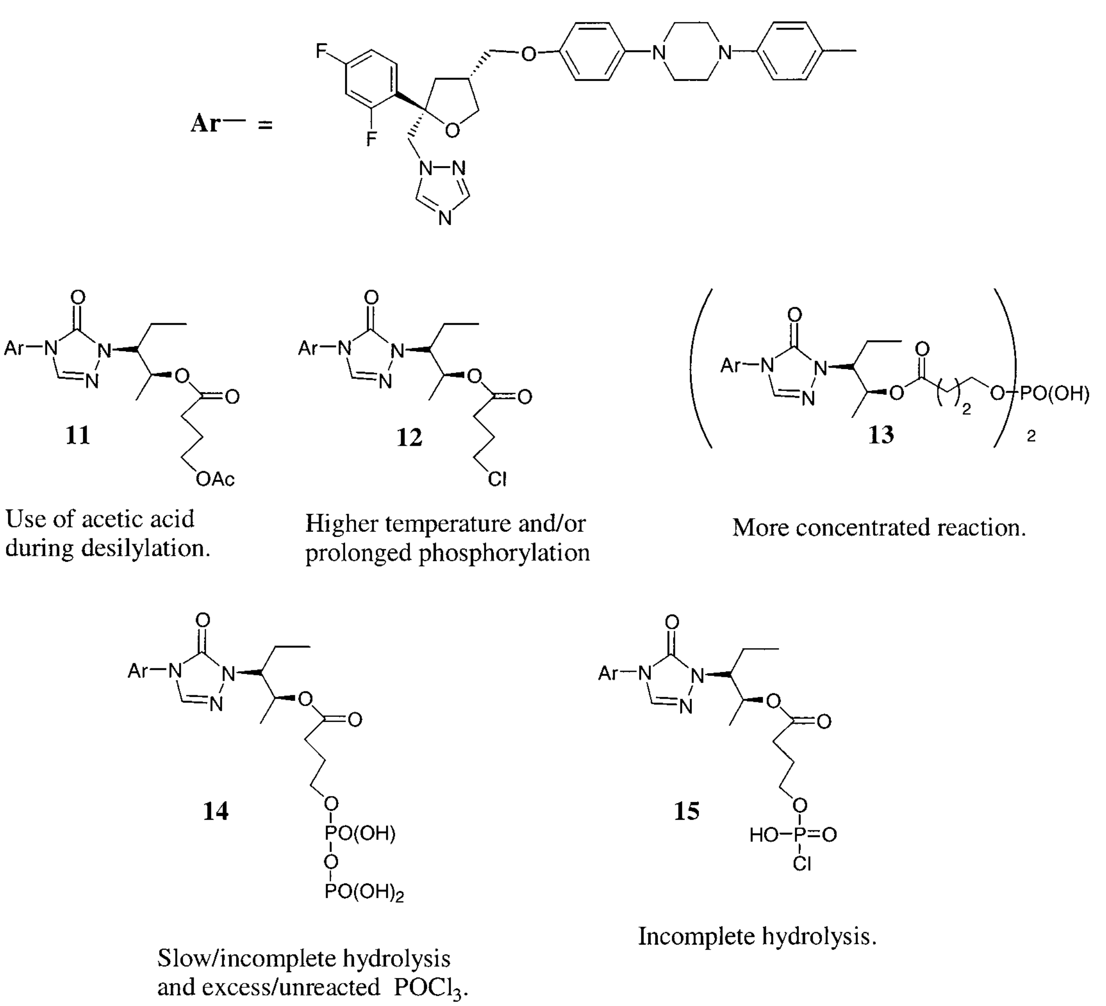
(10) Here desilylation to **9** progressed as expected; however, under the basic conditions created by TBAF, intermediate **9** readily formed λ-lactone and **2**.

(11) Leanza, W. J.; DiNinno, F.; Muthard, D. A.; Wilkening, R. R.; Wildonger, K. J.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron* **1983**, *39*, 2513.



11 Use of acetic acid during desilylation.

12 Higher temperature and/or prolonged phosphorylation

13 More concentrated reaction.

14 Slow/incomplete hydrolysis and excess/unreacted $POCl_3$.

15 Incomplete hydrolysis.

Figure 5. **Impurities and causes for their formation.**

dichlorophosphate intermediate, the uppermost line in Figure 4). Quenching with water on the other hand was a slow reaction and was not complete after 20 min at room temperature. As described below, both the reaction and quenching required optimization for the higher-yielding formation of **1** and minimization of impurities formed due to competing reactions.

To improve the yield, the treatment of **10** with $POCl_3$ had to be conducted under strict temperature control with an exact amount of the reagent. Higher temperature or an excess of reagent led to the formation of **12** or the precursor of **14**. Similarly, the hydrolysis of the dichlorophosphate intermediate formed in this process also needed a high degree of pH and temperature control. Higher temperature, excess of reagents, or a lack of pH control resulted in the formation of 0.5−1.7% impurities **12**−**15** (Figure 5).[12] After careful phosphorylation and hydrolysis, the known crystallization conditions for **1** allowed for the isolation of crystallized **1**, which was identical to that previously reported.[1]

In summary, a novel, intramolecular carboxylate group-to-hydroxyl group silyl transfer for sodium 4-hydroxybutyrate, as well as elucidation of its mechanism, are described.[13] This silyl-transfer discovery was developed into a novel synthesis of injectable antifungal Sch 59884.

Experimental Section

Preparation of Hydroxybutyrate 56592 (10). (a). *tert*-Butyldimethylchlorosilane (TBDMS-Cl) (1.0 equiv) was dissolved in *N*,*N*-dimethylformamide (DMF, 1.67× w/v) and added to a stirred suspension of sodium 4-hydroxybutyrate (1 Mequiv) in DMF (5× w/v) at room temperature; the mixture was stirred at room temperature and monitored by ^1H NMR to determine completion (average 3−4 h); the mixture was diluted with *tert*-butyl methyl ether (TBME), filtered to remove solids, and washed with H_2O; the organic layer was concentrated by half and extracted three times with saturated aqueous sodium bicarbonate ($NaHCO_3$) solution; the basic aqueous layers were combined, washed with toluene, and diluted with TBME; the mixture was agitated, cooled to 10 °C, and the pH was adjusted to between 3.5 and 4.0 with concentrated phosphoric acid (H_3PO_4); the layers were separated, and the aqueous layer was extracted

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[12] These impurities were identified by Drs. L. Heimark and P. Shipkova via HPLC/MS. These impurities in large amounts interfered with the preparation of the water-soluble pharmaceutically acceptable salt of **1**. This, coupled with the previously established specification of **1**, required that these impurities be minimized during the formation of **1** and that they be efficiently purged during crystallization of **1**.

[13] For alternate preparations of 4-*O*-silyloxybutyric acids **8a**−**c**, see: (a) Tori, M.; Toyoda, N.; Sono, M. *J. Org. Chem.* **1998**, 63, 306. (b) Konchel, P.; Lutjens, H.; Klement, I. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1454. (c) Binns, F.; Roberts, S. M.; Taylor, A.; Williams, C. F. *J. Chem. Soc., Perkin Trans. I* **1993**, 800.

with TBME; the combined organic layers were concentrated under reduced pressure to give the product **8a** as a colorless oil; typical yields ranged from 75 to 85%.

(b). Sch 56592 (**2**, 1 Mequiv), **8a** (1.3 Mequiv from step a), and *N′*,*N′*-(dimethylamino)pyridine (DMAP, 3 Mequiv) were dissolved in tetrahydrofuran (THF, 20× v/w compared to **2**) and cooled to 0 °C; *p*-toluenesulfonyl chloride (1.5 Mequiv) was dissolved in THF (12.5× v/w compared to pTS-Cl) and added dropwise to the prior solution, while maintaining the temperature <5 °C; the mixture warmed to room temperature slowly and was monitored for completion by HPLC; after 24 h, the mixture was filtered to remove solids (DMAP-HCl) and concentrated to an oil; the oil was dissolved in ethyl acetate (EtOAc) and washed with a 10% aqueous citric acid solution; the aqueous layer was extracted with EtOAc; the combined organic layers were washed with a saturated brine solution and concentrated to afford an off-white solid. The solid was triturated with hot hexanes, cooled, and filtered to afford the product as an off-white solid; typical yields ranged from 95 to 99%. HRMS for **9**: Calcd for $C_{47}H_{63}N_8O_6F_2Si$: 901.4608. Observed 901.4581.

(c). The product from the previous step was dissolved in THF (10×, v/w) and cooled to 0 °C; a 5% v/v aqueous hydrochloric acid (HCl, 1 Mequiv) solution was added dropwise over 45 min, maintaining temperature below 5 °C; the solution was warmed to room temperature and stirred for 2 h while being monitored for completion by HPLC; the solution was diluted with isopropyl acetate (*i*-PrOAc, 10×) and quenched by the addition of a 2:2:1 saturated $NaHCO_3$: saturated brine:H_2O solution (3× volume). The layers were separated, and the organic layer was washed with a dilute brine solution (3×); the combined aqueous layers were extracted with *i*-PrOAc (2×); the combined organic layers were concentrated to approximately 1/3 volume and then diluted with heptane (2×) while hot; upon cooling the product precipitated out of solution; the product was collected by filtration, washed with cold *i*-PrOAc, and dried in a vacuum oven to afford a white crystalline solid **10**; typical yields ranged from 85 to 90%. Calcd For $C_{41}H_{48}N_8O_2F_2 \cdot 0.3H_2O$: C 62.58; H 6.13; F 4.8; N 13.78. Observed: C 62.16; H 6.18; F 4.8; N 14.4. Melting Point: 98.5−103.5 °C.

Preparation of 59884 (1). Compound **10** (1 Mequiv) from the above step was dissolved in THF and cooled to −30 °C; 1.4 equiv of phosphorus oxychloride ($POCl_3$) dissolved in THF (2.5× v/w compared to **10**) were added dropwise, while maintaining the temperature <−25 °C; The reactions were monitored by HPLC; upon completion (∼4 h), the reaction solutions were quenched by the addition of a 3:1 THF:H_2O (4×) solution, and warmed to room temperature over 45 min. Solid $NaHCO_3$ was added, and the mixture stirred at ambient temperature overnight; the mixture was diluted with a 1:1 solution of brine and dilute aqueous HCl (pH = 2); the layers were separated, and the organic layer was washed with the pH 2 brine solution; the combined aqueous layers were extracted with methylene chloride (CH_2Cl_2); the combined organic layers were dried over anhydrous magnesium sulfate ($MgSO_4$), filtered, and concentrated to afford Sch 59884 as a white solid, identical to the one described in the literature.[1] Typical yields were 75−80%.

To commercialize this process at some facilities it was necessary to avoid the use of environmentally restricted CH_2Cl_2. For this purpose an alternate procedure was developed. Here the reaction in THF was quenched with water as described above and then treated several times with NaCl, followed by saturated NaCl to remove most of water and aqueous HCl form the mixture. This mixture was then subjected to the THF/DME crystallization procedure described previously.[1] This led to the desired product in 55−60% step yield.[14]

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(14) The isolated product contained ∼1.5% NaCl and ∼1.6% (HPLC area) pyrophosphate **14**.