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Aqueous Phosphoric Acid as a Mild Reagent for Deprotection of *tert*-Butyl Carbamates, Esters, and Ethers

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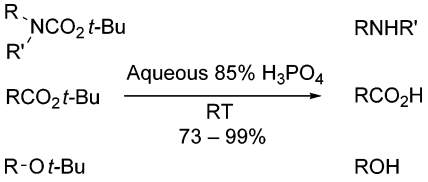

Aqueous phosphoric acid (85 wt %) is an effective, environmentally benign reagent for the deprotection of *tert*-butyl carbamates, *tert*-butyl esters, and *tert*-butyl ethers. The reaction conditions are mild and offer good selectivity in the presence of other acid-sensitive groups, including CBZ carbamates, azetidine, benzyl and methyl esters, TBDMS, and methyl phenyl ethers. The mildness of the reaction is further demonstrated in the synthesis of clarithromycin derivative **4**, in which a *tert*-butyl ester is removed in the presence of cyclic carbamate, lactone, ketal, acetate ester, and epimerizable methyl ketone functionalities. The reaction preserves the stereochemical integrity of the substrates. The reactions are high yielding, and the workup is convenient.

Introduction

One of the important aspects of "green chemistry" is to reduce or eliminate the use of toxic and/or hazardous reagents in the chemical processes.[1] Phosphoric acid (H_3PO_4) is considered a "green" reagent as it is environmental benign and worker friendly. It is widely used in industries of agriculture[2] and consumer products.[3] Pure phosphoric acid is odorless and presents no harm to health when greatly diluted, hence it is used as acidulant, flavorant, synergistic antioxidant, and sequestrant in food.[4,5] Anhydrous phosphoric acid (also known as polyphosphoric acid, containing 82−85% P_2O_5) has been used in organic syntheses for cyclizations,[6] acylations,[7] alkylations,[8] and Beckmann rearrangements.[9] Phosphoric acid is known to effect dehydration of secondary and tertiary alcohols.[10,11] Nonetheless, the use of aqueous phosphoric acid (85 wt %) in synthetic applications has been largely unexplored. Herein we wish to report the use of 85 wt % aqueous phosphoric acid for the deprotection of *tert*-butyl carbamates,[12] *tert*-butyl esters, and *tert*-butyl ethers.

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(1) Sheldon. R. A. *Green Chem.* **2005**, *7*, 267−278.
(2) Ali, Y.; Aslam, Z. *Int. J. Environ. Sci. Tech.* **2005**, *2*, 97−98.
(3) Facts and Figures for the Chemical Industry. *Chem. Eng. News* **2003**, *81*, 25.
(4) Such, J. E. *Inorganic and Theoretical Chemistry*, *Vol*. 8, *Supplement* 3: *Phosphorus*; Eldridge, A. A., Dyson, G. M., Welch, A. J. E., Pantony, D. A., Eds.; Wiley-Interscience: New York, 1971.
(5) *The Merck Index*, 12th ed.; Budavari, S., O'Neil, M. J., Smith, A., Heckelman, P., Kinneary, J. F., Eds.; Merck & Co., Inc.: Whitehouse Station, NJ, 1996.
(6) Wright, C.; Ullas, G. V. J. *Labelled Compds. Radiopharm.* **2002**, *45*, 1265.
(7) Matsuda, H.; Torihara, M.; Tamai, Y. PCT Int. Appl. (2002), WO 0100850.
(8) Tsypin, V. G.; Kachala, V. V.; Ugrak, B. I.; Golod, E. L. *Russ. J. Org. Chem.* **2002**, *38*, 90.
(9) Martinez, L. R.; Gustavo, A. Z.; Jose, D.; Ma, E.; Ramirez, A.; Ma, T.; Canas, R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1675.
(10) (a) Bedford, C. T. *Org. React. Mechanisms* **2003**, 35. (b) Spillane, W. J. *Org. React. Mechanisms* **2001**, 37.
(11) (a) Bacquet, C.; Einhorn, J.; Lelandais, D. *J. Heterocycl. Chem.* **1980**, *17*, 831; (b) Gupta, A. K.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1988**, *29*, 6633.
(12) The *N*-BOC deprotection using 85 wt% phosphoric acid was previously communicated: Li, B.; Bemish, R.; Buzon, R. A.; Chiu, C. K.-F.; Colgan, S. T.; Kissel, W.; Le, T.; Leeman, K.; Newell, L.; Roth, J. *Tetrahedron Lett.* **2003**, *44*, 8113−8115.

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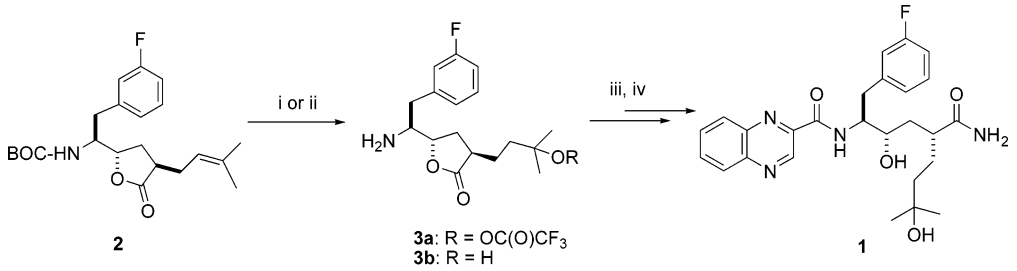
SCHEME 1[a]



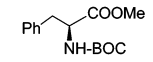
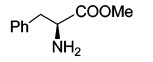
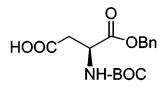
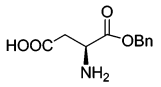
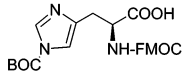
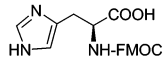
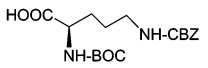
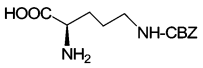
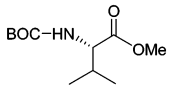
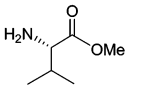
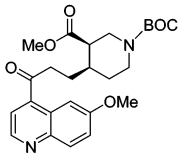
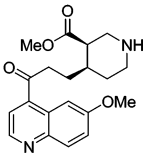
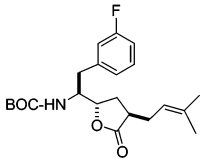
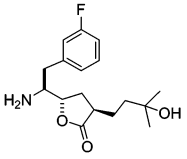
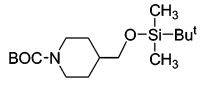
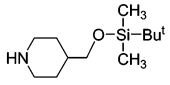
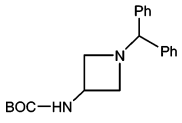
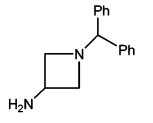
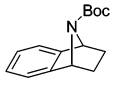
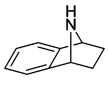
[a] (i) TFA; (ii) aq 85 wt% H_3PO_4; (iii) 2-quinoxaline acid, CDI; (iv) NH_3/MeOH.

Results and Discussion

1. Use of Aqueous 85 wt % H_3PO_4 for *N*-BOC Deprotection. Our initial work with phosphoric acid occurred during the process development[13] of CP-481715 (**1**, Scheme 1), a hydroxyethylene dipeptide isostere that exhibits potent activity against CC-chemokine receptor-1 (CCR1) for the treatment of autoimmune diseases and transplant rejection. The original synthesis of **1**[14] utilized trifluoroacetic acid as solvent to simultaneously remove the *N*-BOC group and hydrate the olefin in **2** to give **3a**. Significant epimerization of the substituent at C-2 in the lactone (~25%) was observed under these reaction conditions. However, when using aqueous 85 wt % phosphoric acid, we observed clean olefin hydration[15] with concomitant deprotection of the *N*-BOC group to give compound **3b**. No epimerization at C-2 was observed in the product. In this reaction, aqueous 85 wt % H_3PO_4 played a role that was irreplaceable by other acids. Typical alkene hydration conditions (i.e., sulfuric acid, nitric acid, or perchloric acid in water)[16] gave the desired product **3b**, but it was invariably contaminated with significant levels of starting material and C-2 epimerization products.

The successful application of aqueous 85 wt % H_3PO_4 in the synthesis of CP-481715 can be ascribed to its higher pK_a. Phosphoric acid is a much weaker acid (pK_{a1} 2.15) than CF_3-COOH (pK_a 0.3), MsOH (pK_a −0.6), TsOH (pK_a −1.3), and other mineral acids.[17] Therefore, it is expected to offer advantages for substrates with acid-sensitive functionalities other than the group to be deprotected. Table 1 summarizes some examples of *N*-BOC deprotection reactions using aqueous 85 wt % phosphoric acid.[18] The reaction works effectively in removing BOC groups from primary and secondary amines, including an imidazole, and exhibits useful chemoselectivity in the presence of other acid-sensitive functional groups. For instance, deprotection in entries 6 and 10 led to degradation of the product when HCl (anhydrous) or TFA was used. Benzyl and methyl esters, *tert*-butyldimethylsilyl ethers, methyl phenyl ethers, and CBZ groups are unaffected under the reaction conditions. No racemization was observed for any of the enantiomerically pure substrates, as determined by chiral HPLC assays.

TABLE 1. Deprotection of *tert*-Butyl Carbamate with Aqueous 85 wt % Phosphoric Acid

Entry	Substrate	Product	Yield[a]
1			90%[19]
2			94%[20]
3			92%[21]
4			95%[22]
5			97%[23]
6			99%[24]
7			78%
8			94%[25]
9			91%[26]
10			90%[27,28]

[a] Isolated yields. All products showed ≥98% purity by HPLC (area percent).

(13) Li, B.; Andresen, B.; Brown, M. F.; Buzon, R. A.; Chiu, C. K.-F.; Couturier, M.; Dias, E.; Urban, F. J.; Jasys, V. J.; Kath, J. C.; Kissel, W.; Le, T; Li, Z. J.; Negri, J.; Poss, C. S.; Tucker, J.; Whritenour, D.; Zandi, K. *Org. Process Res. Dev.* **2005**, *9*, 466−471.

(14) Kath, J. C.; Brown, M. F.; Poss, C. S. PCT Int. Appl. WO 9940061; *Chem. Abstr.* **1999**, *131*, 157767.

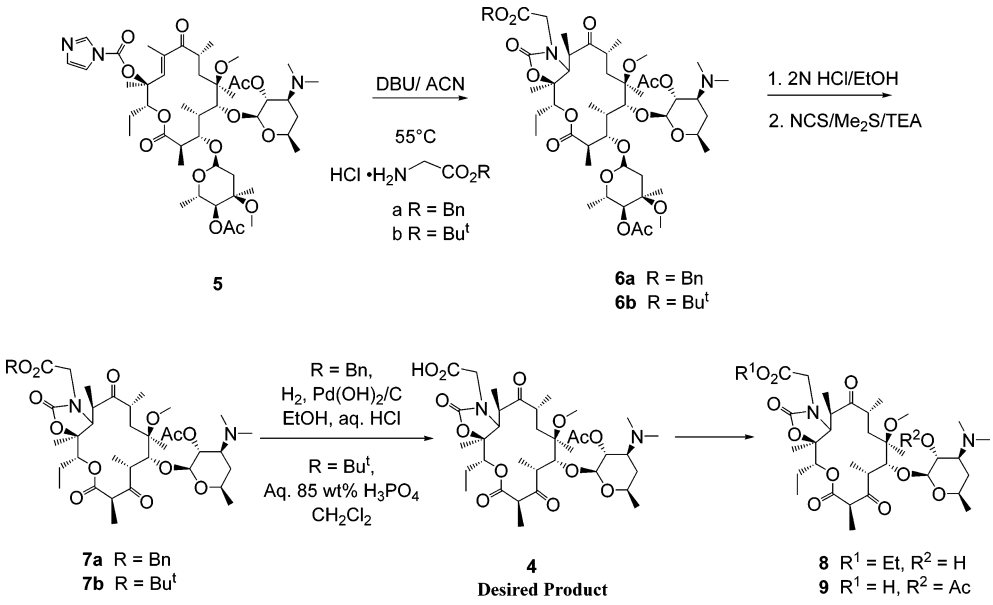
(15) Aqueous 80 wt% phosphoric acid effectively hydrated 4-isopropenephenol: Bader, A. R.; Bean, W. C. *J. Am. Chem. Soc*. **1958**, 3073.

(16) Smith, M. B.; March, J. In *Adv. Org. Chem*., 5th ed.; Wiley and Sons: New York, 2001.

(17) Berkowitz, B. J.; Grunwald, E. *J. Am. Chem. Soc*. **1961**, *83*, 2956.

(18) The deprotection of the *N*-BOC groups using aqueous 85 wt% phosphoric acid was previously communicated: Li, B.; Bemish, R.; Buzon, R. A. Chiu, C. K-F.; Colgan, S.; Kissel, W.; Le, T.; Leeman, K.; Newell, L.; Roth, J. *Tetrahedron Lett.* **2003**, *44*, 8113.

SCHEME 2

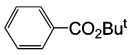
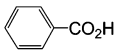
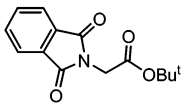
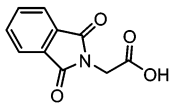
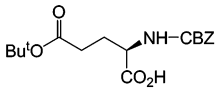
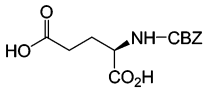
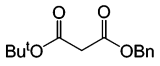
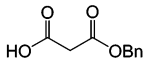
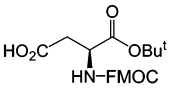
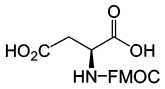
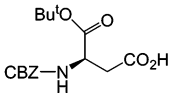
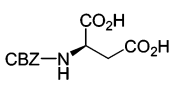
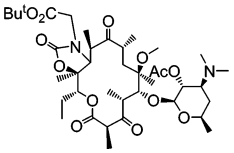
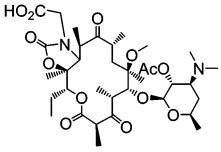


2. Use of Aqueous 85 wt % H_3PO_4 for *tert*-Butyl Ester Deprotection. Our second encounter with aqueous phosphoric acid was during the synthesis of **4** (Scheme 2), a clarithromycin derivative. The original synthesis used benzyl glycinate ester as starting material (Scheme 2, R = Bn). The preparation of intermediate **7a** was relatively straightforward following conditions reported for analogous compounds.[29] However, the deprotection of the benzyl group proved problematic, as the reaction was complicated by two factors. First, the hydrogenolysis required large loading (up to 100% wt/wt) of Perlman's catalyst, which we ascribed to catalyst poisoning by residual methyl sulfide carried over from the previous step (a Corey−Kim oxidation[30]) despite extensive cleanup, including silica gel chromatography, carbon treatment, and recrystillizations. Second, the reaction generated two impurities (**8** and **9**) at significant levels from esterification of the resulting carboxylic acid **4** and hydrolysis of the acetate at the desosamine sugar, respectively. While the formation of **8** was readily resolved by replacing the reaction solvent with THF, levels of byproduct **9** were difficult to control due to the large amount of water carried from both the Pearlman's catalyst and aqueous HCl.[31]

We envisioned that use of *tert*-butyl glycine ester should circumvent the problem, as *tert*-butyl glycine ester is commercially available and deprotection of the *tert*-butyl group was expected to be straightforward. In the event, reaction of *tert*-butyl glycine ester with acyl imidazole **5** provided **6b** uneventfully (Scheme 2, R = Bu^t). The *tert*-butyl ester in **6b** is quite robust and survives[32] the cladinose hydrolysis conditions (2 N HCl/EtOH, 38 °C, 12 h). Oxidation under Corey−Kim conditions provides **7b** in good yields. However, the deprotection of the *tert*-butyl ester proved to be a challenge due to the sensitivity of the macrolide. The use of strong acids, including *p*-toluenesulfonic acid, methanesulfonic acid, trifluoroacetic acid, and formic acid, invariably led to decomposition. Reactions using seemingly milder deprotection method employing $ZnBr_2$[33] turned dark and gave no desired product. This prompted us to explore the use of aqueous 85 wt % phosphoric acid for the deprotection of *tert*-butyl ester **7b**. Our initial attempts (by adding aqueous 85 wt % phosphoric acid to a solution of **7b** in CH_2Cl_2 or acetonitrile) gave incomplete reactions, and a mixture of **7b** and the desired product **4** was obtained upon workup. We determined the cause to be sequestration of unreacted starting material within the large amounts of gummy material (the phosphate salt of **4**) formed during the reaction. By redesigning the reaction by dropwise addition of the substrate solution (**7b** in 1 g/mL of dichloromethane) to a vigorously stirred aqueous 85 wt % phosphoric acid formation of sticky

(19) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, 55, 870−876.
(20) Bryant, P. M.; Moore, R. H.; Pimlott, P. J.; Young, G. T. *J. Chem. Soc*. **1959**, 3868−3873.
(21) Mergler, M.; Dick, F.; Sax, B.; Schwindling, J.; Vorherr, T. *J. Pept. Sci*. **2001**, *7*, 502−510.
(22) Bauer, J.; Martin, R. O.; Rodriguez, S. U.S. Pat. Appl. Publ. US 2005192232; *Chem. Abstr*. *143*, 267243.
(23) Chakraborty, T. K.; Hussain, K. A.; Reddy, G. V. *Tetrahedron* **1995**, *51*, 9179−9190.
(24) (a) Yanuka, Y.; Geryes, A.; Heller. T. *Tetrahedron* **1987**, *43*, 911−922. (b) Malleron, J-L.; Tabart, M.; Carry, J.-C.; Evers, M.; El Ahmad, Y.; Mignani, S.; Viviani, F. PCT Int. Appl. WO 2001025227; *Chem Abstr*. **2001**, *134*, 280720.
(25) Igarashi, Y.; Tanaka, M.; Yanagisawa, E.; Yamaguchi, T. PCT Int. Appl. **1998**, WO 9811086; *Chem. Abstr*. *128*, 230393; (b) Ting, P. C.; Aslanian, R. G.; Berlin, M. Y.; Boyce, C. W.; Cao, J.; Mangiaracina, P.; Mc, Cormick K. D.; Mutahi, M. W.; Rosenblum, S. B.; Shih, N-Y.; Solomon, D. M.; Tom, W. C.; Zeng, Q. PCT Int. Appl. WO 2003103669; *Chem. Abstr*. **2003**, *140*, 27826.
(26) Li, B.; Witt, M.; Brandt, T.; Whritenour, D. *J. Chem. Res*. **2006**, 478−480.
(27) Otani, Y.; Nagae, O.; Naruse, Y.; Inagaki, S.; Ohno, M.; Yamaguchi, K.; Yamamoto, G.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc*. **2003**, *125*, 15191−15199.
(28) For the reaction workup, the reaction mixture was reversely quenched into a mixture of TEA/water/2-MeTHF. This was done to avoid polymerization of the product observed using the forward quench method.
(29) (a) Tanikawa, T.; Asaka, T.; Kashimura, M.; Suzuki, K.; Sugiyama, H.; Sato, M.; Kameo, K.; Morimoto, S.; Nishida, A. *J. Med. Chem*. **2003**, *46*, 2706−2715. (b) Kashimura, M.; Asaka, T.; Misawa, Y.; Matsumoto, K.; Morimoto, S. *J. Antibiot*. **2001**, *54* (8), 664−678.
(30) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc*. **1972**, *84*, 7586−7587.
(31) Use of anhydrous hydrogenolysis conditions did not work well for this deprotection.
(32) By LC−MS, <5% of de-Bu^t intermediate was observed. Nonetheless, the reaction was quenched after the completion of the cladinose hydrolysis due to formation of other impurities (i.e., cleavage of the desosamine sugar).
(33) Kaul, R.; Brouillette, Y.; Sajjadi, Z.; Hansford, K. A.; Lubell, W. D. *J. Org. Chem*. **2004**, *69*, 6131−6133.

TABLE 2. Deprotection of *tert*-Butyl Ester with Aqueous 85 wt % Phosphoric Acid

Entry	Substrate	Product	Yield[a]
1			73%[36]
2			97%[37]
3			98%[38]
4			100%[39]
5			95%[40]
6			74%[41]
7			87%

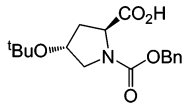
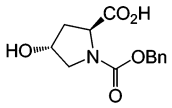
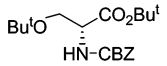
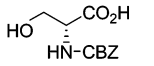
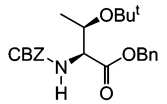
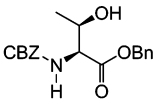
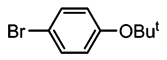
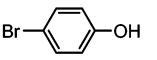
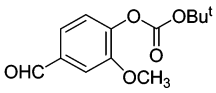
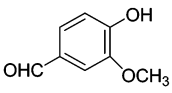
[a] Isolated yields. All products showed ≥98% purity by HPLC (area percent).

precipitates was no longer observed, and the reaction proceeded to completion uneventfully. The reaction was worked up by pH adjustment, followed by extraction with CH_2Cl_2 to give **4** in 87% yield.

The application in the preparation of ketolide intermediate **4** showcased the extraordinary mildness of the reaction conditions using aqueous 85 wt % phosphoric acid. Acid labile functionalities present in the ketolide including the ketal[34] (i.e., the glycosidic bond) and the acetate ester (residing next to dimethylamino group at the desosame) were intact in the reaction. Other functionalities including the cyclic carbamate, the lactone, and epimerizable methyl groups in the macrolide ring were also shown to be compatible. The generality[35] of such application on other *tert*-butyl esters was examined and the results are summarized in Table 2. The reaction gave good to excellent yields of the corresponding carboxylic acids. Acid-labile CBZ and benzyl esters are stable under the reaction conditions.

3. Use of Aqueous 85 wt % H_3PO_4 for *tert*-Butyl Ether Deprotection. After demonstrating that aqueous phosphoric acid (85 wt %) can deprotect *tert*-butyl carbamates and esters, naturally we were curious to examine whether the method would work for *tert*-butyl ether deprotection. It was not surprising that aqueous 85 wt % phosphoric acid was equally effective in cleaving *tert*-butyl ethers, as summarized in Table 3. In general, the *tert*-butyl ether cleavage is somewhat slower than the deprotection of the BOC and *tert*-butyl ester groups, and 5 equiv of aqueous 85 wt % H_3PO_4 is typically required.

TABLE 3. Deprotection of *tert*-Butyl Ether and *tert*-Butyl Carbonate with Aqueous 85 wt % Phosphoric Acid

Entry	Substrate	Product	Yield[a]
1			76%[47]
2			74%[48]
3			82%[49]
4			94%[50]
5			97%[51]

[a] Isolated yields. All products showed ≥98% purity by HPLC (area percent).

Deprotection of *tert*-butyl ethers typically involves the use of strong acids (TFA, HBr/AcOH, HCl, etc.) or Lewis acids (Me_3SiI, TBDMSOTf, $TiCl_4$, $ZnBr_2$,[42] and $CeCl_3 \cdot 7H_2O/NaI$[43]). Formic acid[44]is also known to deprotect *tert*-butyl ethers, but reaction with formic acid is much slower than with aqueous 85 wt % H_3PO_4. In a head-to-head study[45] using 1-bromo-4-*tert*-butoxybenzene as substrate (entry 4, Table 3), the phosphoric acid deprotection reaction was completed in 1 h at room temperature, whereas the formic acid reaction only gave ~25%

(34) Tetrahydropyranyl ethers and isopropylidene groups in general are unstable under the aqueous H_3PO_4 reaction condition with limited exceptions, although we also found few exceptions.

(35) One example was found in the literature using aqueous H_3PO_4 to deprotect from a *tert*-butyl pyrrole-3-carboxylate ester: Ross, J. R.; Vishwakarma, L. C.; Sowell, J. W., Sr. *J. Heterocycl. Chem*. **1987**, *24*, 661−665.

(36) Levine, R.; Stephens, J. R. *J. Am. Chem. Soc.* **1950**, *72*, 1642−1644.

(37) Blaney, P.; Grigg, R.; Rankovic, Z.; Thornton-Pett, M.; Xu, J. *Tetrahedron* **2002**, *58*, 1719−1737.

(38) Zhang, S.-D.; Liu, G.; Xia, S-Q.; Wu, P.; Zhang, L. *J. Combinatorial Chem.* **2002**, *4*, 131−137.

(39) Costa, M.; Dalcanale, E.; Dias, F. S.; Graiff, C.; Tiripicchio, A.; Bigliardi, L. *J. Organomet. Chem*. **2001**, *619*, 179−193.

(40) Mehta, A.; Jaouhari, R.; Benson, T. J.; Douglas, K. T. *Tetrahedron Lett*. **1992**, *33*, 5441−5444.

(41) Okamoto, Y.; Aburatani, R.; Kaida, Y.; Hatada, K. *Chem. Lett*. **1988**, *7*, 1125−1128.

(42) Wu, Y-Q.; Limburg, D. C.; Wilkinson, D. E.; Vaal, M. J.; Hamilton, G. S. *Tetrahedron Lett.* **2000**, *41*, 2847.

(43) Bartoli, G.; Bosco, M.; Locatelli, M.; Marcantoni, E.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2005**, *7*, 427.

(44) (a) Paulsen, H.; Adermann, K. *Liebigs Ann. Chem*. **1989**, 751. (b) Howard, N. I.; Bugg, T. D. H. *Bioorg. Med. Chem.* **2003**, *11*, 3083−3099. (c) Breit, B.; Seiche, W. *J. Amer. Chem. Soc.* **2003**, *125*, 6608−6609. (d) Eguchi, M.; Shen, R. Y. W.; Shea, J. P.; Lee, M. S.; Kahn, M. *J. Med. Chem.* **2002**, *45*, 1395−1398.

(45) One gram of the substrate in 1 mL of acetonitrile using 5 equiv of either formic acid or aqueous 85 wt% H_3PO_4 at room temperature.

conversion after 24 h. Greene and Wuts[46] have described the *tert*-butyl ether as "one of the more underused alcohol protecting groups considering its stability", which has typically been attributed to the operational inconvenience of its introduction (i.e., use of gaseous isobutylene) and limited choices for its deprotection. A convenient method for the installation of *tert*-butyl ether was recently introduced by Bartoli et al.[43] using $(BOC)_2O$ in the presence of $Mg(ClO_4)_2$. The phosphoric acid deprotection method reported herein is an attractive alternative for accomplishing *tert*-butyl ether cleavage. Not surprisingly, the protocol also works well for *tert*-butyl carbonate deprotection (Table 3, entry 5).

In a typical experimental procedure, 85 wt % aqueous phosphoric acid is added to a solution of the reaction substrate in an organic solvent (THF, acetonitrile, toluene or methylene chloride). Typically, a solvent of good solubility for the substrate is chosen. The mixture is vigorously stirred at room temperature until the reaction was complete (monitored by HPLC, typically 3−14 h). Water is added to dilute the reaction mixture, and sodium hydroxide solution is added to adjust the pH to 7−8 (pH adjustment is not necessary for carboxylic acid products). After extractive workup and removal of solvent, the product obtained is typically >98% purity by HPLC assay without further purification. The reaction is conducted at high concentration, typically with 1 mL of solvent/g[52] of substrate, using 2.5−5.0 equiv of 85 wt % aqueous phosphoric acid. The use of a larger amount of organic solvent is undesirable, as it generates a biphasic reaction mixture that slows down the reaction significantly. When no other acid-sensitive functional groups are present, the reaction can be heated (50 °C, 2 h, entries 1 and 2, Table 2). We have noted that at higher reaction temperature (50 °C), methyl and benzyl esters suffer from partial deprotection. The use of a large excess[53] of aqueous 85% H_3PO_4 is unnecessary, as it does not appear to increase the rate of the reaction. If the reaction mixture is biphasic, effective mixing is critical in driving the reaction to completion within reasonable time frames (3−14 h). Nonetheless, use of phase transfer catalysts is not recommended, as it complicates product isolation in many cases.

When pH adjustment is needed for the workup, we have found that concentrated aqueous NaOH (50% solution in water) is most convenient. The resultant aqueous layer is almost fully saturated with sodium phosphate (formed in the pH adjustment), which enhances the product partition in the organic phase. Sodium phosphates formed in the workup also act as a pH buffer, which effectively prevents the pH of the mixture from going too high in case of overcharge of the NaOH solution. This feature is advantageous in production settings where use of a pH probe is not readily applicable.

Conclusion

In conclusion, aqueous phosphoric acid (85 wt %) can be used as an alternate reagent for the deprotection of *tert*-butyl carbamates, esters, and ethers. While the method lacks selectivity among *tert*-butyl carbamates, esters and ethers, it is compatible with many other acid-sensitive functionalities, including the CBZ group, azetidine, methyl and benzyl esters, TBDMS, and methyl phenyl ethers. It is noteworthy that it effected the removal of the *tert*-butyl ester in a clean manner in the synthesis of ketolide intermediate **4** in the presence of acid labile glycosidic bond and acetate ester while all other conditions tried failed.

Aqueous H_3PO_4 is more economical than many other acids[54] commonly used in deprotection of *tert*-butyl carbamates, esters, and ethers. It is environmentally benign and presents no safety hazards to laboratory and pilot plant personnel. In fact, the concomitant removal of *N*-BOC group and hydration of olefin using aqueous H_3PO_4 was employed in production scale for the manufacture of 36 kg of CP-481715 (**1**).

Experimental Section

General Procedure for *N*-BOC Deprotection. 3-Amino-1-benzhydrylazetidine (Entry 1, Table 9). To a solution of *tert*-butyl 1-benzhydrylazetidin-3-ylcarbamate (1.0 g, 2.95 mmol) in CH_2Cl_2(1 mL) at room temperature was added aqueous phosphoric acid (85 wt %, purchased from Aldrich Chemical Co.) (0.51 mL, 7.39 mmol) dropwise. The mixture was vigorously stirred for 3 h, and HPLC assay showed reaction completion.Then 5 mL of water was added and the mixture was cooled to 0 °C. A 50 wt % NaOH solution was added slowly (**Caution:** *exothermic*) to adjust to the pH to ∼8. The mixture was then extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phase was dried over magnesium sulfate and concentrated in vacuo to give the desired product as a white solid (0.64 g, 91%). The product showed 98.7% HPLC purity (by area percent), and coeluted with an authentic sample. NMR and MS spectra were identical to those generated from an authentic sample.

(3*R*,5*S*)-5-((*S*)-1-Amino-2-(3-fluorophenyl)ethyl)-dihydro-3-(3-hydroxy-3-methylbutyl)furan-2(3*H*)-one (Table 1, Entry 7). The crude compound **2**[13] (79.2 g, 202.2 mmol) was stirred with 78 mL of toluene and 300 mL of 85% phosphoric acid with good agitation. After 7 h, the reaction was complete. The mixture was cooled to 0 °C after diluting with water (300 mL), and 50% NaOH was added until the pH was in the range of 7−8.5. Ethyl acetate was added (900 mL), and the layers were separated. The organic solution was dried over magnesium sulfate and concentrated to an oil under vacuum to give 48.8 g (157.8 mmol, 78%) of the product as an colorless oil: MS *m*/*z* (API-ES) 310 $(M + H)^+$, 292 $(M + H - H_2O)^+$. Anal. Calcd. for $C_{17}H_{24}FNO_3$: C, 66.00; H, 7.82; F, 6.14; N, 4.53. Found: C, 65.86; H, 7.95; F, 6.03; N, 4.41. NMR characterization is available in the Supporting Information.

General Procedure for *tert*-Butyl Ester Deprotection. Benzyl Malonate (Table 2, Entry 4). To a solution of benzyl *tert*-butyl malonate (1.5 g, 6.0 mmol) in toluene (1.5 mL) at room temperature) was added aqueous phosphoric acid (85 wt %, purchased from Aldrich Chemical Co. 2.05 mL, 30 mmol) dropwise. The mixture was stirred for 6 h, and HPLC assay showed the reaction was complete. Water (30 mL) was added, and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined ethyl

(46) Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; pp 65−67.

(47) Liu, Y.-T.; Wong, J. K.; Tao, M.; Osterman, R.; Sannigrahi, M.; Girijavallabhan, V. M.; Saksena, A. *Tetrahedron Lett.* **2004**, *45*, 6097−6100.

(48) Lall, M. S.; Ramtohul, Y. K.; James, M. N. G.; Vederas, J. C. *J. Org. Chem.* **2002**, *67*, 1536−1547.

(49) Ross, D. L.; Skinner, C. G.; Shive, W. *J. Org. Chem.* **1959**, *24*, 1440−1442.

(50) Ganguly, N. C.; De, P.; Dutta, S. *Synthesis* **2005**, *7*, 1103−1108.

(51) Gerstenberger, B. S.; Konopelski, J. P. *J. Org. Chem.* **2005**, *70*, 1467−1470.

(52) For reactions on a milligram scale, typically 0.5 mL of the solvent and 0.5 mL of aqueous 85 wt% H_3PO_4 were used so that adequate stirring of the mixture could be ensured.

(53) For the concomitant hydration of the olefin and deprotection of **2** in the synthesis CP-481715, a large excess of aqueous 85 wt% H_3PO_4 (15 equiv) was needed.

(54) Sulfuric acid in CH_2Cl_2 appears to be another economical option when no other acid-sensitive groups are present: Strazzolini, P.; Misuri, N.; Polese, P. *Tetrahedron Lett.* **2005**, *46*, 2075−2078.

acetate phase was dried over magnesium sulfate and concentrated in vacuo to give the desired product as a white solid (1.16 g, 100%). The product showed 99.2% HPLC purity (by area percent) and coeluted with an authentic sample. NMR and MS spectra were identical to those generated from an authentic sample.

Benzoic Acid (Table 2, Entry 1). To *tert*-butylbenzoic acid (1 g, 5.61 mmol) in CH_3CN (1 mL) at room temperature was added aqueous phosphoric acid (85 wt %, 1 mL, 14.6 mmol). The mixture was stirred vigorously for 14 h. Water (5 mL) was added, and the mixture was stirred for 30 min and filtered. The filter cake was rinsed with water (2 × 2 mL) and dried under vacuum to give 0.50 g of the product (4.09 mmol, 73%). The product coeluted with an authentic sample by HPLC. NMR and MS spectra were identical to those generated from an authentic sample.

General Procedure for *tert*-Butyl Ether Deprotection: ***N*-Benzyloxycarbonyl-L-serine (Table 3, Entry 2).** To a solution of *N*-benzyloxycarbonyl-*tert*-butyl-L-serine *tert*-butyl ester (1.0 g, 2.59 mmol) in CH_2Cl_2 (1 mL) at room temperature was added aqueous phosphoric acid (85 wt %, 0.82 mL, 13 mmol) dropwise. The mixture was stirred for 14 h, and HPLC assay showed the reaction was complete. Then 30 mL of water was added. The mixture was extracted with ethyl acetate (3 × 20 mL). The combined ethyl acetate phase was dried over magnesium sulfate and concentrated in vacuo to give the desired product as an oil (0.70 g, 82%). The product showed 98.1% HPLC purity (by area percent) and coeluted with an authentic sample. NMR and MS spectra were identical to those generated from an authentic sample.

4-Bromophenol (Table 3, Entry 4). To 1-bromo-4-*tert*-butoxybenzene (1.21 g, 5.28 mmol) in CH_2Cl_2 (1.2 mL) at room temperature was added aqueous phosphoric acid (85 wt %, 1.21 mL, 19.2 mmol) dropwise. The reaction was stirred at room temperature for 14 h and diluted with water (10 mL). The mixture was extracted with ethyl acetate (3 × 20 mL). The combined ethyl acetate phase was dried over magnesium sulfate and concentrated in vacuo to give the desired product as a white solid (858 mg, 4.96 mmol, 94%). The product showed 99.4% HPLC purity (by area percent) and coeluted with an authentic sample. NMR and MS spectra were identical to those generated from an authentic sample.

2'-*O*-Acetyl-11-*N*-carboxymethy-11,12-cyclocarbamate Ketolide 4. In a 5-L, three-necked round-bottom flask, 300 g of **5**[29] and 60.9 g of *tert*-butyl glycine hydrochloride were stirred in ACN (3 L). DBU (149.4 mL) was added and the reaction mixture was heated to 60 °C for 2.5 h. LC−MS analysis confirmed the reaction was complete. The reaction was concentrated to ca. one-third of the original volume by vacuum distillation, cooled to room temperature, and stirred overnight. IPE (500 mL) was added and the resulting slurry was filtered. The filter cake was dried under vacuum to give 160.9 g of **6b** as crude product.

Then 155.2 g of the crude **6b** obtained was added to a mixture of ethanol (931 mL) and 2 N HCl solution (931 mL), the resulting mixture was heated to 38 °C for 3 h. LC−MS analysis confirmed the reaction was complete. The reaction mixture was quenched into a solution of IPE (1 L), water (1 L), and TEA (155 mL) at 10 °C. The layers were separated, and the organic layer was dried over $MgSO_4$. Evaporation of solvent under vacuum gave a foamy solid, which was dissolved in CH_2Cl_2 (735 mL).

NCS (51.2 g) in CH_2Cl_2 (735 mL) was cooled to −10 °C. Me_2S (32.2 mL) was added dropwise to keep the reaction temperature below −10 °C. The solution of the above product was slowly added to maintain the reaction temperature below −10 °C. The reaction was stirred for 1 h, and TEA (31 mL) was added slowly at a rate to keep the pot temperature below −10 °C. The reaction mixture was then quenched into a cooled solution of EtOAc (1 L) and aqueous saturated $NaHCO_3$ (1 L) at 10 °C. The layers were separated. The CH_2Cl_2 layer was washed with brine solution, dried over $MgSO_4$, and concentrated to an oil under vacuum. The crude oil was passed through flash silica gel (600 g) eluting with 10% MeOH in CH_2Cl_2. The desired cuts were combined and concentrated to afford 109.1 g of **7b** as an oil.

7b obtained (101 g) was dissolved in CH_2Cl_2 (100 mL), and this was added dropwise to a mixture of aqueous 85 wt % H_3PO_4 and CH_2Cl_2 under very vigorous stirring with a mechanical stirrer at room temperature. After 2.5 h, LC−MS analysis confirmed the reaction was complete. The reaction was worked up by decanting off the dichloromethane layer, the aqueous phase was diluted with water (1 L), and EtOAc (1 L) was added. The pH of the aqueous phase was adjusted with the addition of triethylamine to 8.0. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 250 mL). The combined organics were dried over $MgSO_4$ and concentrated under vacuum to afford 81.8 g of **4** as waxy solids: MS *m*/*z* (ESI) 713.5 $(M + H)^+$; HRMS calcd for $C_{35}H_{57}N_2O_{13}$ 713.3861, found 713.3864. Full NMR characterization of **4** is available in the Supporting Information.

Supporting Information Available: Characterization and spectroscopic data for compounds in Tables 1−3. This material is available free of charge via the Internet at http://pubs.acs.org.

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