Published in final edited form as:

Tetrahedron. 2009 January 10; 65(2): 456–460. doi:10.1016/j.tet.2008.10.062.

Triphenylphosphine Dibromide: A Simple One-pot Esterification Reagent

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Abstract

We report a one-pot, expedient protocol for the conversion of carboxylic acids to their esters using excess triphenylphosphine dibromide, base, and the alcohol. The reaction gave the esterified product in moderate-to-high yields (30–95%). For chiral acids, the reaction proceeded with little or no racemization. Use of a chiral alcohol in this transformation gave the ester with retention of configuration of the stereogenic center. Information is presented indicating that esterification proceeds through the intermediate generation of an acyloxyalkoxyphosphorane and where steric interactions play an important role in the energetics of the reaction.

1. Introduction

Esterification reactions are among the oldest and most often used reactions in organic chemistry.¹ Numerous and diverse methods have been advanced for this transformation, assuring that most esters can be prepared. Nonetheless, a simpler, general method would facilitate future synthetic studies.

We sought a readily available esterification reagent that could convert carboxylic acids to their alkyl esters. We report herein that treating aliphatic and aromatic acids with triphenylphosphine dibromide² (**1**), an excess of the primary, secondary, or tertiary alcohols, and a base provided the esterified products in a one-pot reaction. For optically active aliphatic acids, esterification proceeded with little or no racemization. Use of a chiral alcohol in this reaction gave the ester with retention of configuration of the stereogenic center. The conditions and scope of the esterification reactions provided information on the probable pathway for these transformations.

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2. Results and discussion

We first examined aliphatic acids and used 3-phenylpropionic acid (**2**) as the prototype. Treatment of **2** with **1** (5 equiv), K_2CO_3 (11 equiv), and excess MeOH (148 equiv) at room temperature (1 d) gave the esterified product **3a** in 79% yield after purification (Table 1). Substitution of primary alcohols (EtOH, *n*-BuOH, allyl alcohol, 2-chloroethanol, 2-methoxyethanol) for MeOH provided the corresponding esters **3b–3f** in 45–95% isolated yields. Similarly, the secondary alcohol, *i*-propanol, gave ester **3g** in 88% yield. Finally, use of *t*-BuOH produced ester **3h** in 63% yield. Our finding that *t*-butyl esters are prepared by this method is important since the acid-sensitive *t*-butyl group has proven to be useful in synthesis.⁴

The effect of the number of equivalents of **1**, K_2CO_3 , and alcohol as well as the reaction conditions on the efficiency of the esterification process was briefly examined (Table 2). Employing the conversion of **2** to **3b** as a test case, we observed lower yields of the esterified product (40–42%) compared with the 95% yield for **3b** listed in Table 1 as we decreased either the number of equivalents of **1** and K_2CO_3 or the number of equivalents of EtOH (Table 2, entries 1 and 2). Efforts to improve the reaction efficiency by increasing the reaction

temperature or reaction time (Table 2, entries 3 and 4) led to even lower yields of **3b** (Table 2, entries 3 and 4).

We asked the question whether the esterification procedure would proceed without racemization for optically active acids that had a chiral center at the C(α) site. To find out, we treated (*R*)-(-)-2-phenylpropionic acid (**4**), (*S*)-Cbz-phenylglycine (**5**), and (*S*)-Cbz-norvaline (**6**) with **1**, EtOH, and K₂CO₃ (room temperature, 1 d). In all these cases, the reaction gave the optically pure esters **7**⁵ (73% yield, er $\geq$ 96.4%), **8**⁶ (79% yield, er $\geq$ 99.8 %), and **9**⁷ (77% yield, er $\geq$ 97.6 %).⁸

We determined if the esterification of **2** with a secondary, chiral alcohol proceeded with either retention or inversion of the stereogenic center in the alcohol. Using **2** and (*R*)-2-butanol we obtained **3i**⁹ in 82% yield with complete retention of the 2-butoxy unit.

The reaction conditions needed to be modified in order to convert aromatic acids to their esters. Benzoic acid (**10**) served as our test substrate. Acetonitrile was used as the solvent, and reactions containing **10**, **1** (5 equiv), alcohol (5 equiv), and K₂CO₃ (11 equiv) were heated at reflux for 3 d. Moderate yields (35–80%) were obtained for most of the purified products **11** (Table 3). For most unsubstituted alcohols the yields appeared to be largely independent of the alcohol used. However, use of *t*-BuOH in this procedure did not provide ester **11h**. For 2-chloroethanol, we isolated a mixture of the 2-chloroethyl (**11e**) and 2-bromoethyl (**11i**) esters (NMR analysis). Similarly, when we used 2-methoxyethanol we isolated a mixture of the expected ester **11f** along with the corresponding 2-bromoethyl ester **11i** (NMR analysis).

Phosphorus reagents (*e.g.*, dihalophosphoranes, dialkoxyphosphoranes, Wittig reagents, trihalophosphines) have been used extensively in synthesis. In particular, treating carboxylic acids with **1** in aprotic solvents provides the acid halides.^{11–13} Likewise, the dialkoxyphosphoranes and other similarly disubstituted reagents (*e.g.*, bis(2,2,2-trifluoroethoxy)phosphorane,^{14–16} 2,2,2-triphenyl-4,5-(2',2''-biphenylene)-1,3,2-dioxaphospholane,¹⁷ triphenylphosphine thiocyanogen,^{18–22} triphenylphosphine ditriflate²³) have been used to prepare carboxylic acid derivatives.

In Scheme 1, we propose a pathway for the observed esterification reactions. In the initial step, **1** undergoes rapid halide exchange leading either to the monoalkoxy **12** or dialkoxy phosphorane,^{24–26} which can possibly exist in equilibrium with the phosphonium salt **13**. The subsequent attack of **12** by the acid carboxylate provides intermediate **14**,²⁷ which can either react with the alcohol in solution (pathway a) or with the appended phosphorane alkoxy unit by an intramolecular route after pseudorotation to give **14'** to provide the esterified product **16** (pathway b). The pathway in Scheme 1 is similar, in part, to that proposed for the Mitsunobu reaction.²⁸ Unlike most Mitsunobu transformations, we observed retention of the stereogenic center in **3i**.⁹ We also discovered that **2** was converted to ester **3h** with *t*-BuOH (Table 1). Recently, Anders and coworkers have conducted a density functional analysis of the Mitsunobu reaction providing a rationale for both the typical inverted product and the atypical retention adduct.³⁰ Significantly, these investigators suggested that the retention product stems from an acyloxyalkoxyphosphorane species similar to **14** that undergoes Berry pseudorotation and intramolecular substitution.

The pathway outlined in Scheme 1 is consistent with the reported ease with which dihalophosphoranes react with alcohols,^{24–26} and phosphorane-mediated mechanisms that activate carboxylic acid derivatives toward nucleophilic substitution reactions.^{11–13,31,32} Several experimental observations supported the proposed pathway and provided insights into the controlling factors that governed this transformation. First, the yields for **3c** were independent of the order in which reagents were added. For example, we obtained **3c** in 63% yield after we added **1** to a reaction mixture consisting of **2**, *n*-BuOH, and K₂CO₃. Similarly, **3c** was produced in 70% yield after we premixed **1**, *n*-BuOH, and K₂CO₃ for 20 min before adding **2**. These results are consistent with the initial reaction of **1** with the alcohol rather than with the carboxylate. Second, we tested whether dialkoxyphosphoranes, similar to intermediate **12**, could convert carboxylic acids to the corresponding ester. Treatment of **2** with diethoxyphosphorane (DTPP, **18**) gave **3b** (85%), thus demonstrating that **18** and similar compounds can serve as esterification reagents. Indeed, the Evans laboratory reported that **18**-treated **19** provided the esterified product **20**.³³ The utility of **18** for ethyl esterification was not further explored. Third, we observed that **2** was converted to ester **3i**⁹ with retention of the stereogenic center in the (*R*)-2-butanoyl group, and that **2** gave ester **3h** with *t*-butanol. These collective findings suggested that the reaction proceeded through intermediate **14**.

The different reactivities of **2** and **10** with **1** prompted us to

determine if either electronic or steric factors governed the esterification process. We esterified *trans*-cinnamic acid (**21**), 3-(3-pyridyl)propionic acid (**22**), and nicotinic acid (**23**) under the same conditions employed for either **2** or **10**. The α,β -unsaturated acid **21** readily reacted with EtOH under the mild conditions used for the aliphatic acid **2** (room temperature, 1 d) to give **24**³⁴ (57%). The 3-pyridyl-substituted aliphatic acid **22** was converted to the ethyl **25a**³⁵ (76%), *i*-propyl **25b** (75%), and *t*-butyl **25c** (30%) esters at room temperature (1 d). Esterification of nicotinic acid (**23**) with EtOH and *i*-propanol required the use of acetonitrile and heat (reflux, 3 d) to give the ethyl **26a**^{36a} (40%) and *i*-propyl **26b**^{36b} (65%) esters, respectively. The esterification yields of **23** were similar to those of **10** (Table 3), demonstrating that substituting the phenyl group in **10** by the electron-deficient pyridine ring in **23** did not markedly affect this transformation. Collectively, these results showed that electronic effects produced by the R-substituent in carboxylic acids (RCO₂H) could not account for the different conditions needed for **2** or **10** esterification. Consistent with this notion, is the finding that the pK_a values³⁷ for **2** and **10** fall within a narrow range (pK_a 4.2–4.4) indicating that under the mild basic conditions of our reactions both carboxylic acids are converted to the carboxylates.

21 R = H
24 R = Et

22 R = H
25a R = Et
25b R = *i*-Pr
25c R = *t*-Bu

23 R = H
26a R = Et
26b R = *i*-Pr

We then asked whether steric factors affected esterification of **2** and **10**. In our proposed pathway (Scheme 1), **14** serves as the central intermediate. This species places the carboxylic acid R-substituent (alkyl, aryl) in proximity to 1 of the 3 phenyl groups in the proposed trigonal-bipyramidal intermediate **14**. X-ray crystallographic studies of disubstituted triphenylphosphoranes^{25,38} show that the 3 phenyl groups are canted with respect to one another. If the esterification reaction proceeds through **14** then the phenyl R-substituent in **10** is likely to undergo an adverse steric interaction with 1 of the 3 phenyl groups in the triphenylphosphorane compared with the aliphatic R-substituent in **2**. We have modeled the **14** intermediate for the **2**, **10**, and **23** transformations using SPARTAN '06 semi-empiric AM1 equilibrium geometry calculations and we found that the energy-minimized values for the central phosphorane intermediate for **10** and **23** to be appreciably higher than **2** (data not shown). To test this hypothesis further, we treated the tertiary-substituted aliphatic acid, 2-methyl-2-phenylpropionic acid (**27**) with **1** and EtOH and compared the ease of esterification of **27** with **4**. We found that **4** converted to the ethyl ester **7** (73%) under mild conditions (room temperature, 1 d) while **27** required acetonitrile and heat (60 °C, 3 d) to provide its corresponding ethyl ester **28**³⁹ (66%). Molecular-modeling studies indicated that the energy minimized value for the intermediate **14** generated from **27** was higher than predicted from either **2** or **4**. These results, taken together, support the proposed pathway for esterification (Scheme 1) and provide evidence that the energetics for the formation of **14** governs the conditions required for esterification.⁴⁰

27 $R = H$

28 $R = Et$

The efficiency of the **1**-mediated esterification reaction was compared with established procedures. We chose (*S*)-Cbz-phenylglycine (**5**) as a test substrate since it contained a commonly used protecting group (Cbz) and a stereogenic center prone to racemization. First, using Fischer esterification conditions⁴¹ (EtOH (115 equiv), HCl (20 equiv), 78 °C, 16 h) we obtained partially racemized ester **29**⁴² in near quantitative yield and where the Cbz-group was removed. Second, when **5** was esterified with EtOH using the mixed anhydride procedure⁴³ (i, isobutyl chloroformate (1.2 equiv), 4-methylmorpholine (1.2 equiv), -78 °C; ii, EtOH (5 equiv), -78 °C–22 °C, 4 h) we obtained partially racemized **8** in 61% yield. Third, addition of thionyl chloride (15 equiv) to a dichloromethane solution containing **5** and a catalytic amount of DMF (40 °C, 2 h), followed by concentration of the reaction mixture and addition of

EtOH⁴⁴ led to a complex product mixture. Finally, treatment of **5** with thionyl chloride (2 equiv) and EtOH (35 equiv) at 22 °C (16 h)⁴⁵ gave optically pure **8** in 93% yield with little or no racemization.

The proposed pathway for esterification of carboxylic acids (Scheme 1) suggests that similar treatment of esters with **1** and alcohols would provide the trans-esterified products. We briefly explored this using acetonitrile as a solvent and a temperature maintained at reflux for 24 h. Treatment of **3a** with **1**, K₂CO₃ (6 equiv) and EtOH (5 equiv) gave **3b** (70%) along with the recovered methyl ester **3a** (<10%). When we substituted *n*-BuOH for EtOH we obtained a

mixture of methyl (**3a**), and *n*-butyl (**3c**) esters in a 1:1.5 ratio, respectively, and an ~60% yield for **3c**.

3. Conclusions

In summary, we report a simple, one-pot experimental protocol for converting alkyl and aromatic acids to their alkyl esters using **1** and that proceeds with little or no racemization. Reagent **1** is commercially available and can be prepared from triphenylphosphine and Br₂ in near-quantitative yields.²⁵ The method relies on in situ conversion of **1** to an alkoxyphosphorane, which serves as the esterification agent. The described one-pot protocol has several important advantages over the conventional two-step procedure which entails converting the acid to the acid halide with **1**,^{11–13} then treating the isolated acid halide with the alcohol. These advantages include the procedure's simplicity as well as eliminating the need to handle and isolate acid halides which are moisture sensitive and are lachrymators,^{11–13} or the use of aprotic solvents to generate the acid halide. Our studies indicate that the reaction is governed, in part, by the energetics that form the initial pentavalent intermediate **14** containing the carboxylate and in which steric interactions have an important role. Finally, the different reactions reported for **1** among functional groups will affect the scope of this esterification process with respect to the permissible R-substituents in the starting acid.

4. Experimental

4.1. General procedures

Unless otherwise noted, all materials were used as received from a commercial supplier without further purification. All reactions were monitored by analytical thin layer chromatography (TLC) plates (Aldrich, Cat # Z12272-6) and analyzed with 254 nm UV light. The reactions were purified by MPLC (CombiFlash Rf) with self packed columns (silica gel from Dynamic Adsorbents Inc., Cat # 02826-25). Known compounds were characterized by ¹H NMR, ¹³C NMR and MS (when possible) and compared to their literature values. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Optical rotations were obtained on a Jasco P-1030 polarimeter. Proton (¹H NMR, 300 MHz) and carbon (¹³C NMR, 75 MHz) nuclear magnetic resonance spectra were taken on a Varian Gemini 2000 spectrometer in CDCl₃. Chemical shifts (δ) were reported in ppm relative to TMS as an internal reference. Coupling constants (*J*) were reported in Hertz (Hz). Peak multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), br (broad), sept (septet) and m (multiplet). The high-resolution mass spectrum was performed on a Bruker Apex-Q 12 Tesla FTICR by Dr. M. Crowe at the University of North Carolina-Chapel Hill, and the low-resolution mass spectra were done on a BioToF-II-Bruker Daltonics spectrometer by Dr. S. Habibi. Microanalysis were provided by Atlantic Microlab, Inc. (Norcross, GA). The yields refer to isolated yields of compounds estimated to be ≥ 95% pure as determined by ¹H NMR.

4.2. General Procedure for the Esterification of Aliphatic Acids **2** and α,β-Unsaturated Acid **21**

Reagent **1** (2.20 g, 5 mmol) was added to an alcoholic solution (6 mL) of K₂CO₃ (1.60 g, 11 mmol) and the acid (1 mmol). The reaction mixture was stirred at room temperature (24 h). The volatiles were removed and H₂O (25 mL) and CH₂Cl₂ (25 mL) were added to the residue. The organic layer was removed and the aqueous layer was washed with CH₂Cl₂ (25 mL). The organic layers were combined and concentrated in vacuo. The residue was purified by Medium Pressure Liquid Chromatography (MPLC) with hexanes as the eluent to obtain a colorless oil. The compounds prepared by this method were consistent with those published. Representative examples follow:

4.2.1. *i*-Propyl 3-(Pyridin-3-yl)propanoate (25b)— R_f = 0.37 (50% EtOAc in hexanes); IR (neat) 2779, 2392, 1731, 1579, 1429, 1376, 1186, 1035, 858, 802, 715 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.20 (d, J = 6.3 Hz, 2 CH_3), 2.61 (t, J = 7.5 Hz, CH_2), 2.95 (t, J = 7.5 Hz, CH_2), 5.00 (sept, J = 6.3 Hz, OCH), 7.22 (dd, J = 4.8, 7.8 Hz, H_5), 7.54 (dt, J = 2.1, 7.8 Hz, H_4), 8.45–8.49 (m, H_2 and H_6); ^{13}C NMR (CDCl_3): δ 21.7 (2 CH_3), 28.1 (CH_2), 35.7 (CH_2), 67.9 (CHO), 123.3, 135.8, 147.7, 149.9 ($\text{C}_5\text{H}_4\text{N}$), 171.8 (C(O)), the remaining pyridine resonance was not detected and is believed to overlap with nearby peaks; MS ($\text{M}+\text{H}^+$)(ESI $^+$) 194.2 [$\text{M} + \text{H}^+$] (calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_2\text{H}^+$ 194.1); Anal. Calcd. for $\text{C}_{11}\text{H}_{15}\text{NO}_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.23; H, 7.88; N, 7.26.

4.2.2. *t*-Butyl 3-(Pyridin-3-yl)propanoate (25c)— R_f = 0.38 (50% EtOAc in hexanes); IR (neat) 2924, 2860, 1727, 1456, 1369, 1254, 1152, 1031, 847, 801, 714 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.41 (s, C(CH_3) $_3$), 2.56 (t, J = 7.8 Hz, CH_2), 2.91 (t, J = 7.8 Hz, CH_2), 7.21 (dd, J = 4.8, 7.8 Hz, H_5), 7.53 (br d, J = 7.8 Hz, H_4), 8.45–8.49 (m, H_2 and H_6); ^{13}C NMR (CDCl_3): δ 28.0 (C(CH_3) $_3$), 28.2 (CH_2), 36.5 (CH_2), 80.7 (OC(CH_3) $_3$), 123.3, 135.8, 147.7, 149.9 ($\text{C}_5\text{H}_4\text{N}$), 171.6 (C(O)), the remaining pyridine resonance was not detected and is believed to overlap with nearby peaks; MS ($\text{M}+\text{H}^+$)(ESI $^+$) 208.2 [$\text{M} + \text{H}^+$] (calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_2\text{H}^+$ 208.1); Anal. Calcd. for $\text{C}_{12}\text{H}_{17}\text{NO}_2 \cdot 0.07\text{H}_2\text{O}$: C, 69.09; H, 8.29; N, 6.71. Found: C, 69.21; H, 8.20; N, 6.32.

4.3. General Procedure for the Esterification of Chiral Acids

Reagent **1** (2.20 g, 5 mmol) was added to an alcoholic solution (6 mL) of K_2CO_3 (0.76 g, 5.5 mmol) and the acid (1 mmol). The reaction mixture was stirred at room temperature (24 h). The volatiles were removed and H_2O (25 mL) and CH_2Cl_2 (25 mL) were added to the residue. The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (25 mL). The organic layers were combined and concentrated in vacuo. The residue was purified by MPLC with hexanes as the eluent to obtain the esters. The compounds prepared by this method were consistent with those published.

4.4. General Procedure for the Esterification of Aromatic Acids **10**, and Acids **21** and **23**

K_2CO_3 (1.60 g, 11 mmol) was added to a CH_3CN solution (6 mL) containing the acid (1 mmol). The mixture was stirred at room temperature (20 min) and **1** (2.20 g, 5 mmol) and the alcohol (5 mmol) were added. The reaction mixture was stirred at reflux (72 h). The volatiles were removed and H_2O (25 mL) and CH_2Cl_2 (25 mL) were added to the residue. The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (25 mL). The organic layers were combined and concentrated in vacuo. The residue was purified by MPLC with hexanes as the eluent to obtain a colorless oil. The compounds prepared by this method were consistent with those published.

4.5. General Procedure for the Esterification of Aliphatic Acids **2** with DTPP (**18**)

DTPP (**18**) (1.76 g, 5 mmol) was added to an alcoholic solution (6 mL) of the acid (1 mmol), and the reaction mixture was stirred at room temperature (24 h). The volatiles were removed and the residue was purified by MPLC with hexanes as the eluent to obtain a colorless oil.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Mr. Pierre Morieux and Ms. Amber M. King (University of North Carolina-Chapel Hill) for helpful discussions and advice, and Professor Michel Gagne (University of North Carolina-Chapel Hill) for his help in the

energy minimization studies. The project was supported by grant RO1N5054112 (HK) from the National Institute of Neurological Disorders and Stroke.

References and notes

1. Otera, J. Esterification Methods. Reactions and Applications. Wiley-VCH; Weinheim, Germany: 2003.
2. Paquette, LA. Encyclopedia of Reagents for Organic Synthesis. Vol. 8. John Wiley; Chichester, England: 1995. p. 5370-5375.
3. (a) Black PJ, Edwards MG, Williams MJ. Eur J Org Chem 2006;4367–4378. (b) Hayashi M, Kawabata H, Yoshimoto K, Tanaka T. Phosphorus, Sulfur, and Silicon 2007;182:433–445. (c) Horiguchi H, Tsurugi H, Satoh T, Miura M. J Org Chem 2008;73:1590–1592. [PubMed: 18193889] (d) Crosignani S, White PD, Linclau B. J Org Chem 2004;69:5897–5905. [PubMed: 15373475] (e) Mukaiyama T, Ichikawa J, Asami M. Chem Letters 1983;293–296. (f) Takahashi S, Cohen LA, Miller HK, Peake EG. J Org Chem 1971;36(9):1205–1209.
4. Stanton MG, Gagne MR. J Org Chem 1997;62:8240–8242. [PubMed: 11671944]
5. Yang H, Henke E, Bornscheuer UT. J Org Chem 1999;64:1709–1712. [PubMed: 11674241]
6. (a) Hang J, Tian SK, Tang L, Deng L. J Am Chem Soc 2001;123:12696–12697. [PubMed: 11741442] (b) Deng L, Hang J, Tang L. US patent 2003/0166963 2003;A1
7. Moriniere JL, Danree B, Lemoine J, Guy A. Syn Commun 1988;18:441–444.
8. Use of 11 equivalents of K_2CO_3 instead of 5 led to no detectable loss in the optical purity of 7.
9. Lin YY, Palmer DN, Jones JB. Can J Chem 1974;52:469–476.
10. (a) Li LC, Ren J, Liao TG, Jiang JX, Zhu HJ. Eur J Org Chem 2007;1026–1030. (b) Pouchert, C.; Behnke, J. Aldrich FT-NMR Chemical Co. Aldrich Chemical Co.; Milwaukee, WI: 1993. (c) Faler CA, Joullie MM. Tetrahedron Lett 2006;7229–7231. (d) Guo Q, Miyaji T, Hara R, Shen B, Takahashi T. Tetrahedron 2002;58:7327–7334. (e) Wiseman RL, Johnson SM, Kelker MS, Foss T, Wilson IA, Kelly JW. J Am Chem Soc 2005;127:5540–5551. [PubMed: 15826192] (f) Hans JJ, Driver RW, Burke SD. J Org Chem 2000;65:2114–2121. [PubMed: 10841671] (g) Chen CT, Kuo JH, Pawar VD, Munot YS, Weng SS, Ku CH, Liu CY. J Org Chem 2005;70:1188–1197. [PubMed: 15704950]
11. Bestmann HJ, Mott L. Liebigs Ann 1966;693:132–133.
12. Naora H, Ohnuki T, Nakamura A. Chem Letters 1988;143–144.
13. Aizpurua JM, Palomo C. Synthesis 1982;684–687.
14. Kubota T, Kitazume T, Ishikawa N. Chem Letters 1978;889–892.
15. Kubota T, Miyashita S, Kitazume T, Ishikawa N. Chem Letters 1979;845–846.
16. Kubota T, Miyashita S, Kitazume T, Ishikawa N. J Org Chem 1980;45:5052–5057.
17. Kelly JW, Robinson PL, Evans SA Jr. J Org Chem 1986;51:4473–4475.
18. Tamura Y, Kawasaki T, Yasuda H, Gohda N, Kita Y. J Chem Soc Perkin I 1981;1577–1581.
19. Iranpoor N, Firouzabadi H, Shaterian HR. J Chem Res (S) 1999;676–677.
20. Iranpoor N, Firouzabadi H, Shaterian HR. Tetrahedron Lett 2002;43:3439–3441.
21. Iranpoor N, Firouzabadi H, Shaterian HR. Syn Commun 2002;32:3653–3657.
22. Pritchard KM, Al-Rawi JM, Hughes AB. Syn Commun 2005;35:1601–1611.
23. Hendrickson JB, Schwartzman SM. Tetrahedron Lett 1975;4:277–280.
24. Herr ME, Johnson RA. J Org Chem 1972;37:310–312.
25. Mathieu-Pelta I, Evans SA Jr. J Org Chem 1994;59:2234–2237.
26. Wiley GA, Rein BM, Hershkowitz RL. Tetrahedron Lett 1964;36:2509–2513.
27. (a) Burton DJ, Koppes WM. J Org Chem 1975;40:3026–3032. (b) Shintou T, Mukaiyama T. J Am Chem Soc 2004;126:7359–7367. [PubMed: 15186175]
28. (a) Hughes, DL. Organic Reactions. Beak, P., et al., editors. Vol. 42. John Wiley & Sons, Inc.; New York: 1992. p. 335-656. (b) But TYS, Toy PH. Chem Asian J 2007;2:1340–1355. [PubMed: 17890661]
29. For other examples of Mitsunobu reactions proceeding with retention of the alcohol stereogenic center, see: (a) Dinsmore CJ, Mercer SP. Org Lett 2004;6:2885–2888. [PubMed: 15330639] (b) Liao X, Wu Y, De Brabander JK. Angew Chem Int Ed 2003;42:1648–1652. (c) Smith AB III, Safanov

- IG, Corbett RM. *J Am Chem Soc* 2002;124:11102–11113. [PubMed: 12224958] (d) Ahn C, Correia R, DeShong P. *J Org Chem* 2002;67:1751–1753. [PubMed: 11895388] (e) Ahn C, DeShong P. *J Org Chem* 2002;67:1754–1759. [PubMed: 11895389]
30. Schenk S, Weston J, Anders E. *J Am Chem Soc* 2005;127:12566–12576. [PubMed: 16144404]
31. Burton DJ, Koppes WM. *J Chem Soc, Chem Commun* 1973:425.
32. (a) Smissman EE, Alkaysi HN, Creese MW. *J Org Chem* 1975;40:1640–1641. (b) Chaturvedi D, Mishra N, Mishra V. *Tetrahedron Lett* 2007;48:5043–5045.
33. Kelly, JW. PhD Dissertation. University of North Carolina; Chapel Hill: 1986.
34. Chandrasekhar S, Reddy GPK, Nagesh C, Reddy CR. *Tetrahedron Lett* 2007;48:1269–1271.
35. Amatore M, Gosmini C, Périchon J. *J Org Chem* 2006;71:6130–6134. [PubMed: 16872196]
36. (a) Sambrook MR, Beer PD, Wisner JA, Paul RL, Cowley AR, Szemes F, Drew MGB. *J Am Chem Soc* 2005;127:2292–2302. [PubMed: 15713109] (b) Srinivasan R, Srinivasa Rao K, Jayachitra G, Ralte SL. *Syn Commun* 2006;36:2883–2886.
37. Weast, Robert C. *Handbook of Chemistry and Physics*. Vol. 54. CRC Press; Cleveland, Ohio: 1974. p. D-129-D-130.
38. Barnes NA, Godfrey MS, Halton RTA, Law S, Pritchard RG. *Angew Chem Int Ed* 2006;45:1272–1275.
39. Raber DJ, Gariano P Jr, Brod AO, Gariano A, Guida WC, Guida AR, Herbst MD. *J Org Chem* 1979;44:1149–1154.
40. A similar adverse steric interaction may exist after Berry pseudorotation of 14 to 14' prior to intramolecular attack to give the esterified product.
41. Fischer E, Speier A. *Chem Ber* 1895;28:3252–3258.
42. (a) Duhamel L, et al. *Tetrahedron* 1988;44:5495–5506. (b) O'Donnell MJ, Bennett WD, Jacobsen WN, Ma Y, Huffman JC. *Tetrahedron Lett* 1989;30:3909–3912.
43. Anderson GW, Zimmerman JE, Callahan FM. *J Am Chem Soc* 1967;89:5012–5017. [PubMed: 6074804]
44. Bennacer B, Rivalle C, Grierson DS. *Eur J Org Chem* 2003:4569–4574.
45. Brenner M, Huber W. *Helv Chim Acta* 1953;36:1109–1115.

Scheme 1.
Proposal Pathway for **1**-Mediated Esterification Processes

Table 1

Esterification **2** to give **3**^a

Entry	Alcohol	Product	Purified Yield (%) ^b
1	MeOH	3a ^c	79
2	EtOH	3b ^d	95
3	<i>n</i> -BuOH	3c ^e	63
4	CH ₂ =CHCH ₂ OH	3d ^f	53 ^g
5	ClCH ₂ CH ₂ OH	3e ^h	82
6	MeOCH ₂ CH ₂ OH	3f ⁱ	45
7	<i>i</i> -PrOH	3g ^d	88
8	<i>t</i> -BuOH	3h ^c	63

^a All reactions were conducted by treating **2** with an excess of alcohol (6 mL, 63–148 equiv), **1** (5 equiv), and K₂CO₃ (11 equiv) at room temperature for 1 d.

^b The products were purified by medium-pressure liquid chromatography (MPLC).

^c Reference 3a.

^d Reference 3b.

^e Reference 3c.

^f Reference 3d.

^g Compound **3d** was purified by 2 MPLCs.

^h Reference 3e.

ⁱ Reference 3f.

Table 2

Esterification conditions for the conversion of **2** to **3b**^a

Entry	1 (equiv)	K ₂ CO ₃ (equiv)	Rxn Temp	Rxn Time (h)	Yield (%) ^b
1	2	2	22 °C	24	40
2	5	5	22 °C	24	42
3	5	5	82 °C	24	34
4	5	5	22 °C	72	23

^a All reactions were run in acetonitrile using **2** (1 mmol, 1 equiv) and EtOH (5 equiv).

^b Isolated yields after MPLC.

Table 3

Esterification of **10** to give **11**^a

<div style="display: flex; justify-content: space-around; align-items: center; margin-top: 10px;"> <div style="text-align: center;"> 10 </div> <div>+</div> <div style="text-align: center;"> 1 </div> <div> $\xrightarrow[\text{CH}_3\text{CN, reflux}]{\text{ROH, K}_2\text{CO}_3}$ </div> <div style="text-align: center;"> 11 </div> </div>			
Entry	Alcohol	Product	Purified Yield (%) ^b
1	MeOH	11a ^c	51
2	EtOH	11b ^c	80
3	<i>n</i> -BuOH	11c ^d	35
4	CH ₂ =CHCH ₂ OH	11d ^e	80
5	ClCH ₂ CH ₂ OH	11e ^f + 11i ^g	Mixture
6	MeOCH ₂ CH ₂ OH	11f ^h + 11i ^g	Mixture
7	<i>i</i> -PrOH	11g ^c	55
8	<i>t</i> -BuOH	11h ⁱ	0

^a All reactions were conducted by treating **10** with an excess of alcohol (5 equiv), **1** (5 equiv), and K₂CO₃ (11 equiv) in acetonitrile at reflux for 3 d.^b The products were purified by MPLC.^c Reference 10a.^d Reference 10b.^e Reference 10c.^f Reference 10d.^g Reference 10e.^h Reference 10f.ⁱ Reference 10g.