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Benzoyl Trifluoromethanesulfonate. A Mild Reagent for the Benzoylation of Sterically Hindered Hydroxyls

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Benzoyl trifluoromethanesulfonate (BzOTf) is a highly efficient reagent for the benzoylation of a variety of alcohols under mild conditions. These include hindered secondary and tertiary hydroxyls, phenols, and α-glycols. Sensitive functionality is stable when the reaction is performed in the presence of pyridine. Several unique rearrangements of Lewis acid sensitive compounds were also effected.

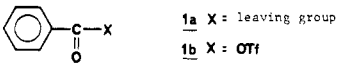
Introduction

Developing efficient and mild methods for the protection of the hydroxyl group continues to be a significant aspect of experimental organic chemistry. Benzoates have been found to be useful as a protecting group for the synthesis of increasingly complicated compounds where protecting group differentiation has become an unavoidable necessity.[1] It has also played a major role in carbohydrate[2a] and nucleoside[2b] protecting group chemistry. Of perhaps greater significance, however, is the current use of benzoates in chiroptical methods for the determination of the absolute stereochemistry of natural as well as synthetic compounds.[3]

Among these chiroptical methods which rely on the benzoate moiety as the key chromophore in their application is the "benzoate sector rule",[4] in which the sector analysis of secondary benzoates has been postulated in order to correlate the sign of the Cotton effect with the absolute configuration of the parent hydroxyl-containing compound. Of more importance are the nonempirical exciton chirality CD methods, such as the "dibenzoate chirality rule",[5] where the sign of the long wavelength Cotton effect can be linked with the chirality of the two benzoate-bearing carbinol C–O bonds. This exciton chirality method was subsequently applied to compounds having an enone benzoate,[6] polyacene benzoate,[7] or diene benzoate moiety.[8] More recently, this same concept has been extended to interactions involving a nonconjugated olefin and an allylic benzoate.[9,10]

We would like to report that benzoyl trifluoromethanesulfonate (benzoyl triflate, BzOTf) is a highly efficient and mild reagent for the benzoylation of hydroxyls in general, particularly sterically congested secondary and tertiary hydroxyls, α-glycols, and phenols. Although the reagent possesses Lewis acid properties, it can be applied to hydroxyl compounds possessing Lewis acid sensitive functionalities when performed in the presence of pyridine. In addition, several synthetically useful transformations will be described that take advantage of these properties.

The methods presently available for the direct[11] benzoylation of alcohols all rely on reagents of the general structure 1 where X, either present in the initial reagent



or generated in situ, is a suitable leaving group. The effectiveness of the reagent depends upon the leaving group ability of X. In this regard, numerous reagents have been developed. Benzoyl chloride in pyridine[1a] remains the most widely used benzoylating agent, especially when the parent

(1) (a) Green, T. W. "Protective Groups in Organic Synthesis"; J. Wiley and Sons: New York, 1981. (b) Haslam, E. *Tetrahedron* **1980**, *36*, 2409.
(2) (a) Hainş, A. H. *Adv. Carbohydr. Res.* **1976**, *33*, 11. (b) Lormann, R.; Khorana, H. G. *J. Am. Chem. Soc.* **1964**, *86*, 4188.
(3) (a) Nakanishi, K.; Harada, N. "Circular Dichroic Spectroscopy - Exciton Coupling in Organic Stereochemistry"; University Science Books: Mill Valley, Ca, 1983. (b) Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *8*, 257.
(4) Nakanishi, K.; Harada, N. *J. Am. Chem. Soc.* **1968**, *90*, 7349.
(5) Nakanishi, K.; Harada, N. *J. Am. Chem. Soc.* **1969**, *91*, 3989.
(6) Koreeda, M.; Nakanishi, K.; Harada, N. *J. Am. Chem. Soc.* **1974**, *96*, 266.
(7) Harada, N.; Nakanishi, K.; Tatsuoka, S. *J. Am. Chem. Soc.* **1969**, *91*, 5896.
(8) Adams, M. A.; Nakanishi, K.; Still, W. C.; Arnold, E. V.; Clardy, J.; Persoons, C. J. *J. Am. Chem. Soc.* **1979**, *101*, 2495.
(9) Gonnela, N. C.; Nakanishi, K.; Martin, V. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1982**, *104*, 3775.
(10) Harada, N.; Iwabuchi, J.; Yokota, Y.; Uda, H.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 5590.
(11) For an indirect method of monobenzoate formation from 1,2-glycols see: (a) King, J. F.; Allbutt, A. D. *Can. J. Chem.* **1970**, *48*, 1754. (b) Koreeda, M.; Akhtar, M. N.; Boyd, D. R.; Neill, J. D.; Gibson, D. T.; Jerina, D. M. *J. Org. Chem.* **1978**, *43*, 1023.

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hydroxyl group is not sterically hindered. Since this reagent is often not suitable for use with sterically congested alcohols, a number of more reactive reagents of the general structure 1 have been developed. These include benzoyl imidazole,[12] benzoyl cyanide,[13] heptafluoro-1-methylethyl phenyl ketone,[14] benzoyl tetrazole,[15] *N,N*-dimethyl[(benzoyloxy)methylene]ammonium chloride,[16] 2-(benzoylthio)-1-methylpyridinium chloride,[17] and 4-(benzoyloxy)pyridine.[18] Likewise, 4-(dimethylamino)-pyridine (DMAP) has proven to be a very active catalyst when used in conjunction with benzoic anhydride in pyridine.[1b,19] However, none of these reagents are *generally* applicable to the benzoylation of tertiary alcohols. In addition, greater than ambient reaction conditions are required for derivatization of hindered alcohols. This frequently leads to undesirable side reactions, such as eliminations or reaction with acid- or temperature-sensitive functionality. Since our initial report,[20] Dauben and coworkers[21] have reported that the reaction of benzoyl chloride in pyridine at 15 kbar for 24–36 h is effective in benzoylating tertiary alcohols and avoids these undesirable side reactions.

Although BzOTf has been known since 1972,[22] its initial[23] and subsequent[24] applications have been limited to that of a highly effective Freidel–Crafts type benzoylating agent for aromatic compounds.[25] This property is ascribable to the highly ionic nature of the ester C–O bond.[26] We reasoned, therefore, that BzOTf should also fit the criteria stated above as an effective benzoylating agent of hydroxyl groups and possibly find application in sterically demanding situations.

Results and Discussion

The benzoylation of secondary alcohols is summarized in Table I. The reaction proceeded in a straightforward manner, as described in the Experimental Section, i.e., the addition of BzOTf to a solution of the alcohol in dichloromethane at −78 °C. Once TLC analysis indicated that the reaction had reached completion, quenching, workup, and chromatography afforded the benzoate product in high yield.

There appears to be a general correlation between the steric environment of the hydroxyl and the yield of the benzoate. For example, the relatively unhindered C-3 hydroxyl position of methyl cholate (**9**) was benzoylated more readily than the C-7 or C-12 hydroxyls, as is evident from the ratio of the product mixture. Isomenthol (**2**) and neomenthol (**3**) exhibit similar behavior.

Table I. Benzoylation of Secondary Hydroxyl Compounds with BzOTf[a]

alcohol	equiv of BzOTf per OH	conditn, temp (°C)/time	yield, %
 **2**	3.0	−78/1 h	68
 **3**	3.0	−78/1 h	77[b]
trans-cyclohexane-1,2-diol (**4**)	1.4	−78/2.5 h	86[c]
cis-cyclohexane-1,2-diol (**5**)	1.4	−78/2.5 h	92[c]
cholesterol (**6**)	1.6	−78/0.5 h	89[d]
6β-hydroxycholest-4-en-3-one (**7**)	5.0	−78/2 h	70[e]
11β-hydroxyandrost-4-ene-3,17-dione (**8**)	3.0	−78/6 min	84
methyl cholate (**9**)	2.0	−78/2.5 h	63[f,g]
17β-estradiol (**10**)	2.2	−78/1 h	72[h,i]
17α-estradiol (**11**)	2.5	−78/1 h	86[j]
17β-estradiol 3-methyl ether (**12**)	3.0	−78/6 min	45[k]

[a] Method A was used for all compounds listed in this table (see Experimental Section). [b] Reference 29. [c] Reference 30. [d] Reference 31. [e] Reference 6. [f] Reference 32. [g] In addition, a mixture of 3,7- and 3,12-dibenzoates (35%) was obtained. [h] Reference 31. [i] The 3-monobenzoate (ref 33) was also isolated in 12% yield. [j] Reference 34. [k] In addition to the 17-benzoate **13**, the 4-benzoyl-17-benzoate **14** was also isolated in ~5% yield.

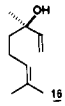
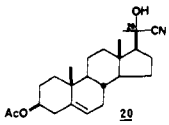
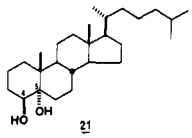
It is noteworthy that the phenolic hydroxyl of 17β- and 17α-estradiols (**10** and **11**) reacted without concomitant Friedel–Crafts type benzoylation being observed. In contrast, 17β-estradiol 3-methyl ether gave rise to a 5:1 mixture of the 17-benzoate and the 4-benzoyl-17-benzoate. This may be due to the difference in the activation of the methyl ether, vis-a-vis the benzoate (generated by reaction of the C-3 hydroxyl with BzOTf) toward electrophilic aromatic substitution. The position of the benzoyl group on the aromatic ring in **12** was based on 360-MHz proton NMR analysis. The 17-benzoate of **12** (**13**) exhibited a doublet at 6.636 ppm (J = 2.7 Hz) and a doublet of doublets at 6.710 ppm (J = 8.6 and 2.7 Hz) corresponding to H-2 and H-4, respectively. For 4-benzoyl-17-benzoyl-**12** (**14**), however, the resonance for H-4 was absent, with H-2 appearing as a doublet at 6.796 ppm (J = 8.6 Hz).

It is interesting to note the stability of the allylic alcohol **7** to the reaction conditions. This is in sharp contrast to other allylic or benzylic alcohols (e.g., **16**, **23**, and **24**), which in the absence of pyridine decomposed, even at −78 °C.

Tertiary alcohols underwent successful benzoylation only in the presence of pyridine. Results are summarized in Table II. Although yields range from fair to good, axial tertiary hydroxyls are generally more reluctant to undergo benzoylation than are equatorial hydroxyls. Comparison of glycol **17** with glycol **18** demonstrates this point. The tertiary equatorial hydroxyl at C-2 of **18** smoothly underwent benzoylation, providing the dibenzoate in 72% yield, whereas the axial tertiary hydroxyl at C-2 of **17** was benzoylated in only 42% yield, along with the corresponding 3-monobenzoate (49%). Furthermore, the axial 5α-hydroxyl in **21**, surrounded by four 1,3-diaxial hydrogens, failed to be benzoylated, even after prolonged reaction times (18 h at room temperature). The cyanohydrin **20** was the only tertiary alcohol to be benzoylated without the addition of pyridine. This may be explained by taking

(12) Staab, H. A.; Mannschreck, A. *Chem. Ber.* **1962**, *95*, 1284.
(13) (a) Holy, A.; Soucek, M. *Tetrahedron Lett.* **1971**, 185. (b) Havel, M.; Velek, M.; Pospisek, J.; Soucek, M. *Collect. Czech. Chem. Commun.* **1979**, *44*, 2443.
(14) Isakawa, N.; Shin-ya, S. *Chem. Lett.* **1976**, 673.
(15) Stawinski, J.; Homuzi, T.; Narang, S. A. *J. Chem. Soc., Chem. Commun.* **1976**, 243.
(16) Stadler, P. A. *Helv. Chim. Acta* **1978**, *61*, 1675.
(17) Yamada, M.; Watabe, Y.; Sakakibara, T.; Sudoh, R. *J. Chem. Soc., Chem. Commun.* **1979**, 179.
(18) Effenberger, F. *Chem. Ber.* **1980**, *113*, 2100.
(19) Hofle, G.; Steglich, W.; Vorbuggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.
(20) Koreeda, M.; Brown, L., *J. Chem. Soc., Chem. Commun.* **1983**, 1113.
(21) Dauben, W. G.; Bunce, R. A.; Gerdes, J. M; Henegar, K. E. *Tetrahedron Lett.* **1983**, *24*, 5709.
(22) Effenberger, F.; Epple, G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 299.
(23) Effenberger, F.; Epple, G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 300.
(24) Effenberger, F.; Sohn, E.; Epple, G. *Chem. Ber.* **1983**, *116*, 1195.
(25) For reports on other reactions of BzOTf generated in situ, see: (a) Martens, H.; Janssens, F.; Hoornaert, G. *Tetrahedron* **1975**, *31*, 177. (b) Minota, H.; Miura, T.; Kobayashi, M. *Chem. Lett.* **1977**, 609. (c) Galli, C. *Synthesis* **1979**, 303.
(26) Effenberger, F. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 151 and references therein.

Table II. Benzoylation of Tertiary Hydroxyl Compounds with BzOTf/Pyridine[a]

alcohol	equiv of BzOTf per OH	equiv of pyridine per OH	yield, %
 15	3.0	4.5	81
 16	2.0	3.6	34[b]
 17	2.5	4.5	42[c]
 18	2.0	3.1	75
 19	3.0	4.8	89
 20	2.0	0	49[d]
 21	2.0	3.0	70[e]

[a] Method B was used for all compounds listed in this table (see Experimental Section) at −78 °C for 0.5 h and then at room temperature for 1 h. [b] Reference 21. [c] In addition, the 3-monobenzoate was isolated in 49% yield. [d] Performed at −40 °C for 0.5 h (see text). [e] Yield of 4-monobenzoate (see text).

into account the electron deficient nature of the tertiary carbon (vide infra).

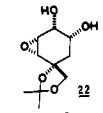
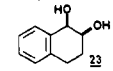
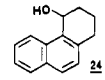
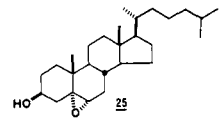
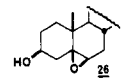
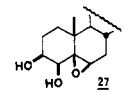
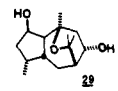
Table III lists examples of substrates possessing Lewis acid sensitive functionality. In the absence of pyridine, alcohols **22**, **26**, and **29** underwent decomposition, resulting in an intractable mixture of unidentified compounds, even at −78 °C. Epoxide **27** and spiroketal **28**, however, cleanly rearranged under the reaction conditions to give products resulting from the reaction between BzOTf and a non-hydroxyl oxygen. These will be discussed later in this report.

These results, indicating enhanced electrophilicity of BzOTf, can be interpreted as due to the highly ionic character of the ester C–O bond in BzOTf. Effenberger has examined[27] a number of aromatic trifluoromethanesulfonic anhydrides, and has found most to be partially dissociated, as evidenced by the acylium ion band in the IR at 2200 cm^{-1} taken in 1,2-dichloroethane. Interestingly, however, the same absorption was not observed for BzOTf. Nonetheless, it can still be assumed that there is a highly ionic character in the ester C–O bond of BzOTf, even at −78 °C. This charge distribution accounts for the high leaving group character of the trifluoromethanesulfonate (triflate) ion, thus making BzOTf such a reactive benzoylating agent, even in the absence of base.

Without exception, the addition of pyridine to the alcohol prior to the addition of BzOTf allowed for the smooth transformation of the hydroxyl to the benzoate in cases where the absence of pyridine led to decomposition. This modified reactivity of BzOTf may be due to the

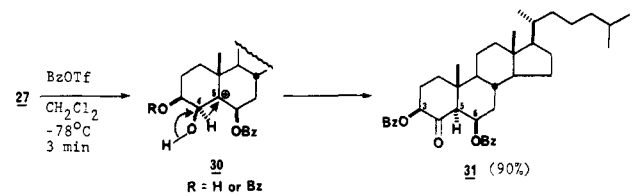
(27) Effenberger, F.; Epple, G.; Eberhard, J. K.; Buhler, U.; Sohn, E. *Chem. Ber.* **1983**, *113*, 1183.

Table III. Benzoylation of Hydroxyl Compounds Containing Lewis Acid Sensitive Functional Groups with BzOTf/Pyridine[a]

alcohol	equiv of BzOTf per OH	equiv of pyridine per OH	yield, %
 22	2.0	3.5	95
 23	2.0	3.6	95[b]
 24	2.0	3.5	71[b]
 25	3.0	4.5	76[c]
 26	3.0	4.5	85[c]
 27	2.0	3.0	90
diosgenin (28)	4.1	6.0	63[d]
 29	2.1	3.6	70[e]

[a] Method B was used for all compounds listed in this table (see Experimental Section). [b] Reference 35. [c] Reference 36. [d] Reference 31. [e] Reference 37.

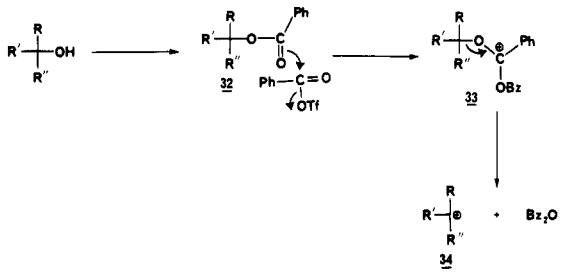
Scheme I



formation of *N*-benzoylpyridinium triflate as the reactive benzoylating species. The formation of *N*-benzoylpyridinium salts is well precedented in the literature and such ion pairs are thought to be responsible for the catalytic activity of 4-(dimethylamino)pyridine with benzoic anhydride.[19] The reaction between BzOTf and pyridine can be assumed substantially faster than the decomposition of Lewis acid sensitive oxygen-based functional groups by BzOTf. The benzoylation of hydroxyl groups with BzOTf and pyridine required longer reaction times and higher temperatures than that by BzOTf alone (see Experimental Section). These observations indicate that *N*-benzoylpyridinium triflate is less reactive in the benzoylation of hydroxyls than BzOTf. Thus, it would be expected that reactivity would also be deminished toward Lewis acid sensitive functional groups. The successful benzoylation of hydroxyls with BzOTf and pyridine without substantial decomposition of Lewis acid sensitive moieties, as listed in Tables II and III, are in accord with this notion.

Treatment of epoxide containing compounds with BzOTf in the absence of pyridine all resulted in decomposition following the initial Lewis acid catalyzed opening of the epoxide ring. Exception to this is the case where the initially generated carbonium ion undergoes rearrangement via epoxide ring opening. Thus, treatment of

Scheme II

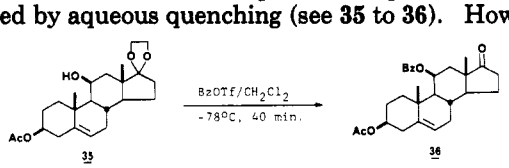


the epoxy diol **27** with BzOTf gave rise to the keto dibenzoate **31**. Proton irradiation experiments at 360 MHz established the unique structure of **31**. The axial C-3 proton appeared at 5.430 ppm as a doublet of doublets with J = 12.4 and 7.3 Hz. Irradiation at the C-3 proton caused no change at either the C-5 or C-6 protons, which appeared at 2.491 ppm (d, J = 12.5 Hz) and 5.694 ppm (ddd, J = 7.6, 2.5 and 2.5 Hz), respectively. However, upon irradiation at 2.491 ppm, the C-6 proton collapsed to a doublet of doublets. Likewise, irradiation at 5.694 ppm simplified the C-5 proton to a singlet. The 90.56-MHz ^{13}C NMR spectrum revealed a ketone carbonyl peak at 201.38 ppm as well as the two expected ester carbonyl resonances at 165.85 and 165.47 ppm. The IR spectrum also differentiated the ester from the ketone carbonyl, revealing bands at 1740 and 1725 cm^{-1}, respectively. The product **31** presumably arose from the carbonium ion intermediate **30**, generated via epoxide opening, followed by hydride shift from C-4 to C-5.

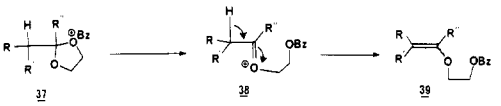
The common feature of all other substrates which were not compatible with BzOTf in the absence of pyridine is the ability to generate a stable carbonium ion upon heterolytic cleavage of the C–O bond in the substrate. This manifests itself as either a tertiary C–O bond, an allylic or benzylic alcohol, or an acetal or ketal where the resulting carbonium ion is stable or resonance stabilized. The extreme lability of either the tertiary or allylic/benzylic hydroxyl moiety is undoubtedly a result of the facile generation of the tertiary or resonance stabilized carbonium ion **34** which would further undergo decomposition (Scheme II). Significantly, in all these cases the formation of benzoic anhydride was confirmed by either TLC or isolation. These observations strongly suggest a mechanism involving the BzOTf-mediated decomposition of an initially formed tertiary or allylic/benzylic benzoate **32** as illustrated in Scheme II.

Exception to the necessity of pyridine in the reaction system for allylic and tertiary alcohols was found in **7** and **20**. In these cases, benzoylation was found to proceed smoothly with BzOTf alone, without an appreciable amount of elimination or decomposition products being observed. A plausible explanation for this stability can be arrived at by examining the electronic factors placed upon the carbon bearing the hydroxyl by adjacent substituents. In both cases, electron-withdrawing groups (enone and cyano, respectively) are present. It would therefore be expected that in these cases, the incipient carbonium ion intermediate (i.e., **34**) is destabilized, resulting in the decreased propensity for decomposition.

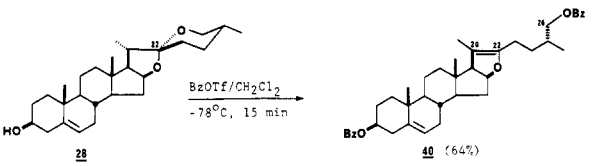
Acetals and ketals generally underwent clean deacetalization and deketalization upon their exposure to BzOTf followed by aqueous quenching (see **35** to **36**). However,



when a trisubstituted carbon was present α to the initially generated oxonium ion double bond carbon (see **37**), loss of the proton from this α carbon took place to give rise to an enol ether **39**. The most illustrative example of this



enol ether formation was the synthesis of pseudodiosgenin dibenzoate (**40**) from diosgenin (**28**). Thus, treatment of diogenin (**28**) with 2.2 equiv of BzOTf in dichloromethane at –78 °C for 15 min resulted in the clean formation of the enol ether dibenzoate **40** in 64% yield. The 360-MHz



proton NMR spectrum of the product showed two sets of aromatic proton peaks as well as a downfield shift of the C-26 protons (AB of the ABX pattern centering at 4.177 ppm with J_{AB} = 10.8 Hz). Likewise, the 90.56-MHz ^{13}C NMR spectrum indicated two quaternary sp^2 carbons at 103.83 and 151.51 ppm, assignable to C-20 and C-22, respectively. This highly efficient side chain degradation method should provide a convenient means for the synthesis of steroid hormone precursors from various sapogenins.[28]

Conclusion

Benzoyl trifluoromethanesulfonate (BzOTf), obtained in one step from inexpensive, commercially available reagents in high yield, has been found to be a highly effective benzoylating agent for a variety of sterically hindered alcohols. These include tertiary, phenolic, and α-glycolic hydroxyls. Highly Lewis acid sensitive functional groups are stable to the reaction conditions when in the presence of pyridine. However, useful synthetic transformations can be effected by taking advantage of the electrophilic nature of BzOTf.

Experimental Section

Benzoyl Trifluoromethanesulfonate (BzOTf).[22] A dry 25-mL round-bottom flask was equipped with a stir bar and rubber septum. After purging with nitrogen, freshly distilled benzoyl chloride (6.4 g, 46 mmol) was added via syringe prior to cooling to 0 °C. Trifluoromethanesulfonic acid (6.8 g, 45 mmol) was slowly added via syringe. The reaction was allowed to slowly warm to room temperature, and after 20 h, the dark solution distilled through a 12-in. Vigreux column under vacuum. After a lower boiling forerun was discarded, the product was collected as a colorless oil (7.5 g, 66% yield): bp 92–94 °C (2.2 mmHg); density 1.51 g/mL at 25 °C.

Benzoylation of Primary and Secondary Alcohols (Method A). The alcohol was added to a dry round-bottom flask, which had been equipped with a stir bar and rubber septum. After purging with dry nitrogen, dry methylene chloride was added to make a 0.1 M solution, and the solution was cooled to –78 °C (dry ice/acetone). The appropriate amount of BzOTf was then added via syringe, and the reaction was monitored by thin-layer chromatography until it had reached completion.

Workup can be accomplished by addition of water (aqueous workup), followed by dilution with ethyl acetate, separation of the aqueous layer, then washing with saturated sodium bicarbonate and brine, and drying over anhydrous sodium sulfate.

(28) Lednicer, L.; Mitscher, L. A. "Organic Chemistry of Drug Synthesis"; Wiley: New York, 1977.

Removal of the solvent at reduced pressure provided the crude product. Alternatively, the reaction can be quenched with a slight excess of methanol (nonaqueous workup), followed by filtration through Florisil with methylene chloride prior to removal of the solvent at reduced pressure. Flash column chromatography[38] gave the purified product.

Benzoylation of Tertiary Alcohols and Hydroxyl Compounds Containing Sensitive Functionality (Method B). The procedure is identical with method A, except ca. 1.5 equiv of dry pyridine, relative to BzOTf, was added to the reaction vessel prior to cooling. After proceeding for 30 min at −78 °C, the solution was allowed to warm to ambience, and after 1 h at room temperature, was quenched and worked up as before.

(+)-Isomenthol Benzoate. Method A was employed with 66 mg (0.42 mmol) of (+)-isomenthol (**2**) and 315 mg (1.27 mmol, 3.0 equiv) of BzOTf for 1 h. The reaction was quenched with methanol. Purification via TLC (20 by 20 cm by 1 mm thick, 2% ethyl acetate/petroleum ether) afforded 74 mg (68% yield) of the benzoate as a clear liquid.

(+)-Neomenthol Benzoate. The same procedure followed as for (+)-isomenthol was applied to 90 mg (0.58 mmol) of (+)-neomenthol (**3**) and 450 mg (1.7 mmol, 3.0 equiv) of BzOTf. The benzoate[29] (110 mg, 0.38 mmol, 77% yield) was obtained after the identical purification as a light oil.

11β-Hydroxyandrost-4-ene-3,17-dione Benzoate. Method A was used in reacting 15 mg (0.050 mmol) of 11β-hydroxyandrost-4-ene-3,17-dione (**8**) with 375 mg (0.15 mmol, 3.0 equiv) of BzOTf. After 6 min, the reaction was quenched with water and worked up as usual. Purification via preparative TLC (20 by 7 cm by 1 mm thick, 1.6% methanol/dichloromethane) gave 17 mg (84% yield) of the benzoate.

Benzoylation of Methyl Cholate (9). Method A was used on 68 mg (0.16 mmol) of methyl cholate (**9**) and 2.4 g (0.97 mmol, 2 equiv) of BzOTf. After 1.5 h, quenching with methanol and purification by TLC gave 75 mg (63% yield) of the 3,7,12-tribenzoate[32] and 36 mg (35% yield) of a mixture of 3,7- and 3,12-dibenzoates.[32]

Benzoylation of 17β-Estradiol (10). To 61 mg (0.22 mmol) of 17β-estradiol (**10**) was added 285 mg (1.1 mmol, 2.5 equiv) of BzOTf, as in method A. The reaction was quenched with water after 2.5 h and then worked up. Purification by preparative TLC (20 by 20 cm by 1 mm thick, 2 developments with benzene, then half the plate developed with 30% ethyl acetate/petroleum ether) gave 77 mg (72% yield) of the 3,17-dibenzoate[31] (mp 151.0–152.0 °C, recrystallized from dichloromethane/methanol) and 10 mg (12% yield) of the 3-monobenzoate[33] (mp 194.0–195.0 °C, recrystallized from methanol).

17α-Estradiol Dibenzoate. 17α-Estradiol (**11**) (49 mg, 0.18 mmol) was treated with 228 mg (0.90 mmol, 5.0 molar equiv) of BzOTf for 1 h, as in method A. The reaction was quenched with water and worked up. Purification by preparative TLC (20 by 20 cm by 1 mm thick, 5% ethyl acetate/petroleum ether) afforded 74 mg (86% yield) of the dibenzoate.[34]

Benzoylation of 17β-Estradiol 3-Methyl Ether (12). When method A was used, 39 mg (0.14 mmol) of 17β-estradiol 3-methyl ether (**12**) and 103 mg (0.41 mmol, 3.0 equiv) of BzOTf afforded, after 6 min and quenching with water, 24 mg (45% yield) of the 17-benzoate **13**, along with a small amount (5 mg) of the 4-benzoyl-17-benzoate **14**, which was purified by TLC (20 by 20 cm by 1 mm thick, benzene, six developments).

1-Methylcyclopentanol Benzoate. When method B was followed, 70 mg (0.70 mmol) of 1-methylcyclopentanol (**15**) was treated with 375 mg (3.1 mmol, 4.5 equiv) of pyridine and 525 mg (2.0 mmol, 3.0 equiv) of BzOTf. Aqueous workup and purification via TLC provided 115 mg (81% yield) of the tertiary benzoate as a liquid.

(−)-Linalool Benzoate. Method B was employed using 115 mg (0.746 mmol) of (−)-linalool (**16**), 215 mg (2.7 mmol, 3.6 equiv) of pyridine, and 380 mg (1.5 mmol, 2.0 equiv) of BzOTf. Quenching with methanol and workup afforded the crude product which was purified by TLC (20 by 20 cm by 1 mm thick, dichloromethane, two developments) to give 66 mg (34% yield) of the tertiary benzoate[21] as a thin oil.

Benzoylation of (2*S*,3*R*,5*R*)-2-Methyl-2,3-dihydroxy-5-isopropenylcyclohexanone (17). The trans diol **17**[39] (61 mg, 0.331 mmol) was benzoylated with 235 mg (3.0 mmol, 9 molar equiv) of pyridine and 420 mg (5 molar equiv) of BzOTf according to method B. After quenching with methanol and the usual workup, purification was done via preparative TLC (20 by 20 cm by 1 mm thick, dichloromethane, three developments). The 2,3-dibenzoate of **17** was obtained in 42% yield (55 mg), along with 47 mg (49% yield) of the 3-monobenzoate, both as viscous oils.

(2*R*,3*S*,5*R*)-2-Methyl-2,3-dihydroxy-5-isopropylcyclohexanone Dibenzoate. The trans diol **18**[39] (40 mg, 0.22 mmol) was treated as in method B with 220 mg (0.86 mmol, 2.0 equiv) of BzOTf and 110 mg (1.4 mmol, 3.2 equiv) of pyridine. The reaction was quenched with methanol and worked up. Preparative TLC (10% ethyl acetate/petroleum ether, two developments) afforded 64 mg (75% yield) of the dibenzoate: mp 128–130 °C.

1-Adamantanol Benzoate. 1-Adamantanol (**19**) (99 mg, 0.65 mmol) was treated with 495 mg (1.95 mmol, 3.0 equiv) of BzOTf and 245 mg (3.1 mmol, 4.8 equiv) of pyridine as in method B. The reaction was quenched with methanol and worked up. Purification by preparative TLC (20 by 20 cm by 1 mm thick, one development with petroleum ether, two developments with 2% ethyl acetate/petroleum ether) gave 148 mg (0.58 mmol, 89% yield) of the product. Recrystallization from methanol gave white needles: mp 66.5–67.0 °C.

Benzoylation of Pregnenolone Acetate 20-Cyanohydrin (20). Method A was used, except that the temperature was maintained at −40 °C in order to circumvent solubility problems. Thus, 102 mg (0.28 mmol) of the cyanohydrin **20**[40] and 143 mg (0.56 mmol, 2.0 equiv) of BzOTf were reacted for 30 min before quenching with methanol. After purification by preparative TLC (20 by 20 cm by 1 mm thick, dichloromethane), the product (64 mg, 49% yield) was obtained as a thick oil.

4β,5α-Dihydroxycholestane 4-Benzoate. Method B was used with 29 mg (0.094 mmol) of 4β,5α-dihydroxycholestane (**21**),[41] 47 mg (0.59 mmol, 6.3 molar equiv) of pyridine, and 95 mg (0.38 mmol, 4.0 molar equiv) of BzOTf. Quenching with methanol, workup, and purification via preparative TLC (20 by 20 cm by 1 mm thick, dichloromethane, two developments) gave 27 mg (70% yield) of the monobenzoate: mp 130.0–131.5 °C (recrystallized from methanol).

Benzoylation of Epoxy Diol 22. The epoxy diol **22**[42] (72 mg, 0.333 mmol), pyridine (190 mg, 2.3 mmol, 7.0 molar equiv), and BzOTf (340 mg, 1.3 mmol, 4.0 molar equiv) were reacted as for method B. After quenching with water, the reaction was worked up. Purification by TLC (20 by 20 cm by 1 mm thick, 1.5% methanol/dichloromethane) afforded 134 mg (95% yield) of the dibenzoate: mp 145.5–146.0 °C (recrystallized from methanol).

3β,4β-Dihydroxy-5β,6β-epoxycholestane Dibenzoate. By employment of method B, the epoxy diol **27**[43] (78 mg, 0.19 mmol) was benzoylated with 104 mg (1.31 mmol, 6.0 molar equiv) of pyridine and 190 mg (0.75 mmol, 4.0 molar equiv) of BzOTf. After the reaction was quenched with methanol, the crude reaction mixture was purified via preparative TLC (20 by 20 cm by 1 mm, 5% EtOH/petroleum ether) to give 105 mg (90% yield) of the

(29) Kato, A.; Ueda, H.; Hasimoto, Y. *Agric. Biol. Chem.* **1970**, *34*, 1843.
(30) Wilson, N. A. B.; Read, J. *J. Chem. Soc.* **1935**, 1269.
(31) "Dictionary of Organic Compounds", fourth ed.; Oxford University Press: New York, 1965.
(32) Gawronski, J.; Gawronska, K.; Kielczewski, M. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1976**, *24*, 267.
(33) Whitman, B.; Wintersteiner, O.; Schwenk, E. *J. Biol. Chem.* **1937**, *118*, 789.
(34) Prelog, V.; Ruzicka, L.; Wieland, P. *Helv. Chim. Acta* **1945**, *28*, 250.
(35) The authentic benzoate was available in these laboratories.
(36) Kocovsky, P.; Cerny, V.; Turecek, F. *Collect. Czech. Chem. Commun.* **1979**, *44*, 234.
(37) Ito, S.; Kodama, M.; Nozoe, T.; Hikino, H.; Hikino, Y.; Takeshita, Y.; Takemoto, T. *Tetrahedron* **1967**, *23*, 553.
(38) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(39) Roelots, W.; Gieselmann, M.; Carde, A.; Tashiro, H., Moreno, D. S.; Henrick, C. A.; Anderson, R. J. *J. Chem. Ecol.* **1978**, *4*, 211.
(40) Byon, C.-y.; Gut, M. *J. Org. Chem.* **1976**, *41*, 3716.
(41) Bergmann, W.; Skau, E. L. *J. Org. Chem.* **1940**, *5*, 439.
(42) Synthesized from (−)-quinic acid for another synthetic program in these laboratories (Dr. S. Takahashi, unpublished results).

dibenzoate: mp 124.0–125.0 °C (recrystallized from methanol).

Kessyl Glycol Dibenzoate. Kessyl glycol (**29**)[37] (75 mg, 0.30 mmol) was treated as in method B with 180 mg (2.2 mmol, 7.5 molar equiv) of pyridine and 315 mg (1.2 mmol, 4.2 molar equiv) of BzOTf. After the usual methanol workup, the product was purified by TLC (20 by 20 cm by 1 mm thick, 0.5% methanol/dichloromethane) to yield 95 mg (70% yield) of dibenzoate:[37] 181.0–182.0 °C (recrystallized from cyclohexane).

3β,6β-Bis(benzoyloxy)-5α-cholestan-4-one (31). The epoxy diol **27**[43] (57 mg, 0.14 mmol) was treated with 150 mg (0.56 mmol, 2.0 equiv) of BzOTf for 3 min, as in method A. After aqueous workup and purification by preparative TLC (20 by 20 cm by 1 mm thick, 0.25% methanol/dichloromethane), 77 mg (90% yield) of the keto dibenzoate **31** was obtained: mp 174.0–175.5 °C (recrystallized from dichloromethane/methanol); ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.686 (3 H, s), 0.859 (3 H, d, J = 6.6 Hz), 0.863 (3 H, d, J = 6.6 Hz), 0.919 (3 H, d, J = 6.5 Hz), 1.267 (3 H, s), 2.309 (1 H, d, J = 3.2 Hz), 2.34–2.41 (1 H, m), 2.491 (1 H, br, d, J = 2.5 Hz), 5.430 (1 H, dd, J = 12.4 and 7.3 Hz), 5.694 (1 H, ddd, J = 2.5, 2.5 and 7.6 Hz), 7.384 (2 H, dd, J = 7.4 and 7.4 Hz), 7.405 (2 H, dd, J = 7.6 and 7.6 Hz), 7.513 (4 H, t, J = 7.4 Hz), 7.986 (2 H, dd, J = 7.9 and 1.4 Hz) and 8.023 (2 H, dd, J = 7.8 and 1.3 Hz); ^{13}C NMR (90.56 MHz, $CDCl_3$) [* indicates unresolved multiplicity] δ 12.24 (q), 18.11 (q), 18.72 (q), 21.61 (t), 22.55 (d), 22.80 (d), 23.86 (*), 24.15 (*), 28.03 (*), 28.13 (*), 28.85 (*), 30.73 (d), 35.77 (t), 36.17 (t), 37.48 (t), 39.53 (t), 39.83 (t), 42.30 (s), 42.71 (s), 54.25 (d), 55.77 (d), 56.31 (d), 58.21 (d), 66.99 (d), 76.26 (d), 128.22 (d), 129.73 (d), 129.89 (d), 131.05 (s), 132.48 (d), 133.03 (d), 165.47 (s), 165.85 (s) and 201.38 (s), three unresolved resonances; IR (CCl_4) 2950 (m), 1740 (m), 1725 (s), 1370 (w), 1270 (s) and 1115 (m) cm^{-1}; MS (CI (CH_4), 23 eV) 609 (0.06%), 505 (5), 383 (5), 123 (100) and 105 (55); $[\alpha]^{27}_D$ −16.2° (*c* 1.485, $CHCl_3$). Anal. Calcd for $C_{41}H_{54}O_5$: C, 78.56; H, 8.68. Found: C, 78.50; H, 8.62.

3β-Acetoxy-11β-(benzoyloxy)androst-5-en-17-one (36). Method A was used on 156 mg (0.399 mmol) of the ketal alcohol **35** and 345 mg (1.44 mmol, 3.0 molar equiv) of BzOTf. After 40 min, aqueous workup and preparative TLC (30% ethyl acetate/petroleum ether) gave 152 mg (85% yield) of the keto benzoate **36** as an oil.

Pseudodiosgenin Dibenzoate (40). To 196 mg (0.473 mmol) of diosgenin (**28**) was added 530 mg (2.1 mmol, 4.4 molar equiv) of BzOTf, as in method A. After 15 min, the reaction was quenched with water and worked up. Flash chromatography, using a gradient elution of 7%, 8%, 10%, and 12% ethyl acetate/petroleum ether, gave 188 mg (0.302 mmol, 64% yield) of the dibenzoate **40**: mp 120.5–122.0 °C (recrystallized from methanol); ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.697 (3 H, s), 1.043 (3 H, d, J = 6.8 Hz), 1.084 (3 H, s), 1.596 (3 H, s), 2.15–2.22 (2 H, m), 2.46–2.50 (2 H, m), 4.145 (1 H, dd, J = 10.8 and 6.5 Hz), 4.208 (1 H, dd, J = 10.8 and 5.7 Hz), 4.743 (1 H, ddd, J = 10.1, 7.8, and 5.7 Hz), 4.87 (1 H, m), 5.420 (1 H, br, d, J = 4.2), 7.41–7.46 (4 H, m), 7.52–7.57 (2 H, m) and 8.03–8.06 ppm (4 H, m); ^{13}C NMR (90.56 MHz, $CDCl_3$) δ 11.63 (q), 13.98 (q), 16.83 (q), 19.41 (q), 21.04 (t), 23.28 (t), 27.93 (t), 30.94 (t), 31.32 (t), 32.26 (d), 32.43 (d), 34.17 (t), 36.83 (t), 37.11 (t), 38.26 (t), 39.56 (t), 43.23 (s), 50.10 (d), 55.04 (d), 69.52 (d), 74.49 (d), 84.38 (d), 103.83 (s), 122.43 (d), 128.23 (d), 128.28 (d), 129.54 (d), 129.55 (d), 130.60 (s), 130.90 (s), 132.66 (d), 132.73 (d), 139.76 (s), 151.51 (s), 165.94 (s) and 166.58 (s), five unresolved resonances; IR (CCl_4) 2950 (m), 1720 (s), 1270 (s) and 1115 (m) cm^{-1}; MS (CI (CH_4), 23 eV) 623 (M^+ + 1, 15), 622 (M^+, 3.7), 502 (17), 501 (53), 285 (32), 253 (28), 229 (55), 163 (21), 123 (55) and 105 (100); $[\alpha]^{27}_D$ −11.6° (*c* 0.790, $CHCl_3$). Anal. Calcd. for $C_{41}H_{50}O_5$: C, 79.06; H, 8.08. Found: C, 78.87; H, 7.99.

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Registry No. **1b**, 36967-85-8; **2**, 23283-97-8; **2** (benzoate), 91840-42-5; **3**, 2216-52-6; **3** (benzoate), 31481-49-9; **4**, 1460-57-7; **4** (dibenzoate), 53226-58-7; **5**, 1792-81-0; **5** (dibenzoate), 37854-29-8; **6**, 57-88-5; **6** (benzoate), 604-32-0; **7**, 570-89-8; **7** (benzoate), 52118-34-0; **8**, 382-44-5; **8** (benzoate), 88722-93-4; **9**, 1448-36-8; **9** (tribenzoate), 60918-29-8; **9** (3,7-dibenzoate), 88722-97-8; **9** (3,12-dibenzoate), 88722-98-9; **10**, 50-28-2; **10** (dibenzoate), 4147-13-1; **10** (3-benzoate), 50-50-0; **11**, 57-91-0; **11** (dibenzoate), 88722-94-5; **12**, 1035-77-4; **13**, 4828-26-6; **14**, 91798-48-0; **15**, 1462-03-9; **15** (benzoate), 88722-95-6; **16**, 126-91-0; **16** (benzoate), 91781-99-6; **17**, 91782-00-2; **17** (dibenzoate), 91782-01-3; **17** (3-benzoate), 91782-02-4; **18**, 79194-65-3; **18** (dibenzoate), 91840-43-6; **19**, 768-95-6; **19** (benzoate), 38584-43-9; **20**, 22641-61-8; **20** (benzoate), 91782-03-5; **21**, 20233-47-0; **21** (4-benzoate), 91782-04-6; **22**, 91782-05-7; **22** (dibenzoate), 91782-06-8; **23**, 21016-53-5; **23** (dibenzoate), 75125-39-2; **24**, 56179-82-9; **24** (benzoate), 91782-07-9; **25**, 1250-95-9; **25** (benzoate), 51646-05-0; **26**, 4025-59-6; **26** (benzoate), 6557-19-3; **27**, 50727-96-3; **27** (dibenzoate), 91782-11-5; **28**, 512-04-9; **29**, 6894-57-1; **29** (dibenzoate), 91798-49-1; **31**, 88722-99-0; **35**, 91782-08-0; **36**, 91782-09-1; **40**, 91782-10-4.

Supplementary Material Available: Information regarding general methods and spectroscopic and microanalytical data of 17 selected benzoyl products (7 pages). Ordering information is given on any current masthead page.

(43) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.