Synthetic Methods

A Mild and Selective Method for the Hydrolysis of Esters with Trimethyltin Hydroxide**

K. C. Nicolaou, Anthony A. Estrada, Mark Zak, Sang Hyup Lee, and Brian S. Safina*

The mild and selective hydrolysis of esters can often be crucial in the sequence toward a target molecule and is, therefore, an important objective in contemporary organic synthesis. Although several methods exist to accomplish this task in certain cases, a mild, generally applicable protocol remains absent. Frequent problems encountered include the concurrent hydrolysis of other ester groups present within the molecule under scrutiny, epimerization of stereocenters, and elimination reactions induced by the often basic conditions employed. Herein we report a new and selective method for the hydrolysis of esters under extremely mild conditions that avoid such side reactions and lead to high yields of the corresponding carboxylic acids.

It was during our campaign toward thiostrepton,[1] a highly complex thiopeptide antibiotic, that we had the opportunity to search for such a method. Our sensitive intermediates proved too fragile to tolerate standard ester hydrolysis conditions. We finally came upon Me_3SnOH, which had been previously employed by Mascaretti and co-workers[2] to cleave phenacyl ester anchored amino acids and peptides from a polystyrene resin and to hydrolyze methyl and isopropyl phenylacetate to give the corresponding acids in high yield. To our knowledge, these are the only examples in which Me_3SnOH has been previously used to carry out hydrolytic ruptures of esters.[3] As shown in Table 1, this reagent proved extremely useful to us in attaining the high-yielding and selective hydrolysis of methyl esters within the sensitive substrates **1**–**4**, which were encountered en route to thiostrepton. These remarkable results prompted a second-phase investigation in which we attempted to determine systematically the generality and scope of this protocol, which involved heating the substrate with 1–10 equivalents of

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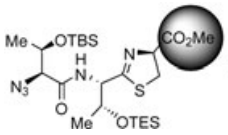
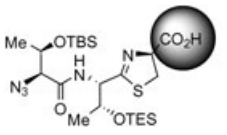
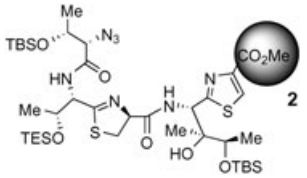
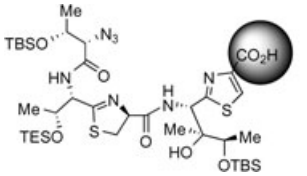
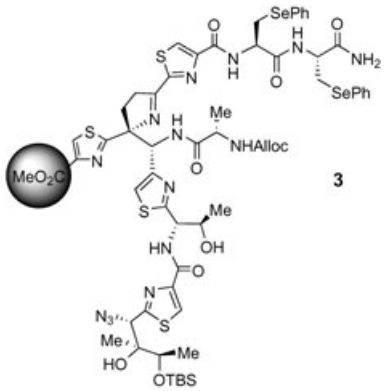
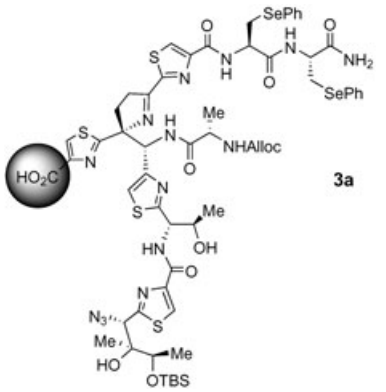
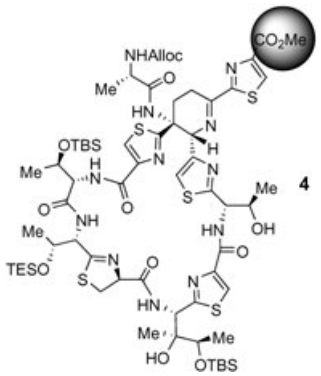
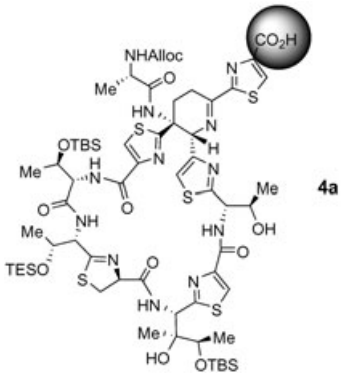
Table 1: Trimethyltin hydroxide mediated hydrolyses used in the total synthesis of thiostrepton.[a]

Entry	Ester	Product(s)	*T* [°C]	*t* [h]	Yield [%]
1	 **1**	 **1a**	80	1	100
2	 **2**	 **2a**	80	2.5	100
3	 **3**	 **3a**	80	3	85
4	 **4**	 **4a**	60	2.5	100

[a] Reactions were carried out in 1,2-DCE on a 0.04–0.25-mmol scale and worked up as described in the general procedure. Alloc = allyloxycarbonyl; Boc = *tert*-butoxycarbonyl; DCE = 1,2-dichloroethane; TBS = *tert*-butyldimethylsilyl; TES = triethylsilyl.

Me_3SnOH in 1,2-dichloroethane at 60–80 °C. Table 2 shows the results of this second investigation.

Whereas the successful hydrolysis of **5** (Table 2, entry 1) with LiOH had been previously reported,[4] our attempt to reproduce these results on a larger scale resulted in significant epimerization at the azide-bearing stereocenter. Application of the Me_3SnOH conditions to substrate **5** yielded the desired product **5a** in excellent yield and without undesired epimerization. The usefulness of the mild Me_3SnOH reagent with substrates sensitive to epimerization was further illustrated in the hydrolyses of thiazolines **6** and **7** (Table 2, entries 2 and 3), in which the pure carboxylic acids were isolated in 85 and 88 % yield, respectively. Equally intriguing was the fact that the Fmoc protecting group in **6** remained intact throughout the hydrolysis, an achievement that was not attainable with other methods, and one that was further supported by the successful hydrolysis of Fmoc-D-Ala (**21**) to its corresponding carboxylic acid (**21a**) with complete retention of the Fmoc protecting group (Table 2, entry 17). In contrast, upon treatment of **21** with LiOH, partial cleavage (≈33 %) of the Fmoc group was observed by the time hydrolysis of the methyl ester was complete. The hydrolyses of methyl ester **8** (Table 2, entry 4) and allyl ester **9** (Table 2, entry 5) under standard LiOH conditions revealed only decomposition, which most likely stems from side reactions with the phenyl selenium groups. In contrast, application of the new procedure generated the desired products **8a** and **9a** (physical properties, Table 4) in excellent to quantitative yields. The α,β-keto ester **10** (Table 2, entry 6) provided yet another challenging substrate for the tin reagent. Again, the use of LiOH resulted in decomposition, but when Me_3SnOH was employed the expected carboxylic acid **10a** (physical properties, Table 4) was isolated as the major component in 77 % yield, with the minor product formed from intramolecular 1,4-addition of

Table 2: Trimethyltin hydroxide mediated hydrolysis of esters and related compounds.[a]

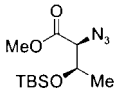
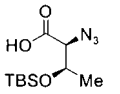
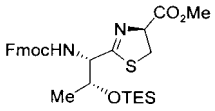
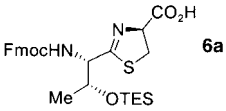
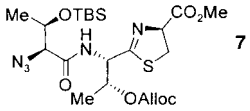
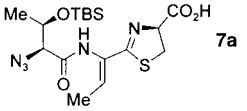
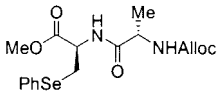
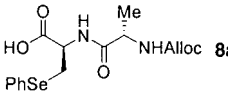
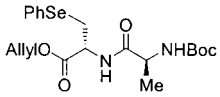
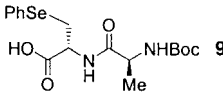
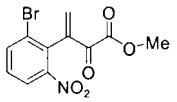
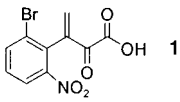
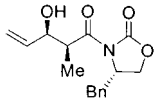
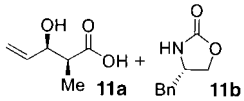
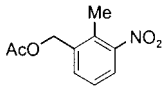
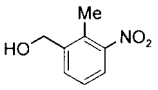
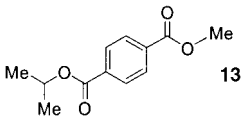
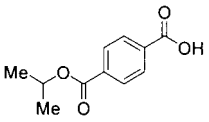
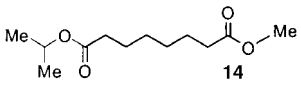
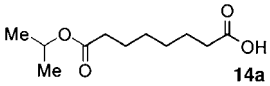
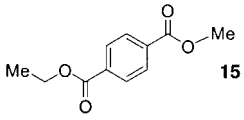
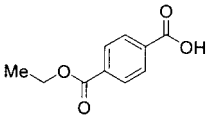
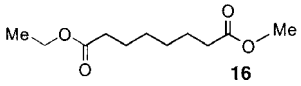
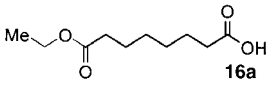
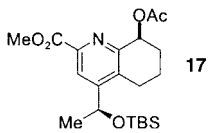
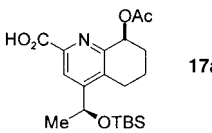
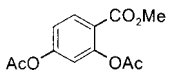
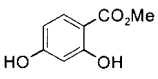
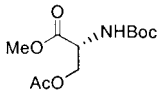
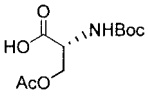
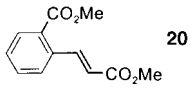
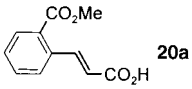
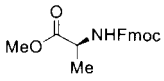
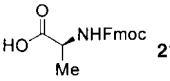
Entry	Ester	Product(s)	*T* [°C]	*t* [h]	Yield [%]	Selectivity[b]
1	 **5**	 **5a**	80	3	98	–
2	 **6**	 **6a**	70	1	85	–
3	 **7**	 **7a**	80	2	88	–
4	 **8**	 **8a**	80	1	87	–
5	 **9**	 **9a**	80	2	100	–
6	 **10**	 **10a**	80	1	77	–
7	 **11**	 **11a** + **11b**	80	7	84	–
8	 **12**	 **12a**	80	2	100	–
9	 **13**	 **13a**	80	5	80	≈90:1
10	 **14**	 **14a**	80	7	82	≈10:1
11	 **15**	 **15a**	70	9	70	≈10:1
12	 **16**	 **16a**	70	10	70	≈3:1
13	 **17**	 **17a**	80	2	67	–
14	 **18**	 **18a**	80	5	100	–
15	 **19**	 **19a**	80	2	80	–

Table 2: (Continued)

Entry	Ester	Product(s)	T [°C]	t [h]	Yield [%]	Selectivity[b]
16	 **20**	 **20a**	80	9	70	≈7:1
17	 **21**	 **21a**	80	5	75	–

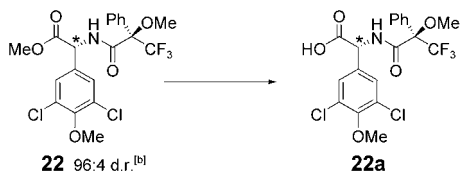
[a] Reactions were carried out in 1,2-DCE on a 0.04–0.15-mmol scale and worked up as described in the general procedure. Bn = benzyl; Fmoc = 9-fluorenylmethoxycarbonyl. [b] For the methyl ester.

the resulting carboxylic acid group to the proximate Michael-acceptor olefin. The scope of this method was further expanded when it was discovered that Me_3SnOH could cleave the Evans oxazolidinone chiral auxiliary[5] (**11b**) from aldol product **11** to afford carboxylic acid **11a** in good yield (Table 2, entry 7). The generality of the method with regards to other esters also proved to be quite good, as it was successful in cleaving methyl, ethyl, allyl, and benzyl esters, but ineffective toward pivaloate esters. Substrate **12** (entry 8, Table 2) further illustrates the efficiency of this protocol in cleaving acetate esters in quantitative yields.

Entries 9–16 in Table 2 demonstrate the selectivity of this method. It is evident that the methyl ester is hydrolyzed preferentially over isopropyl and ethyl esters in good yield, for both aromatic and aliphatic systems. A small amount of diacid is also produced in these reactions; in these cases it is a consequence of the partial susceptibility of the isopropyl and ethyl esters to the conditions of the reaction. In testing the selectivity for benzyl versus methyl esters and allyl versus methyl esters, it was found that no significant preference prevailed. In testing the selectivity between acetate protecting groups and methyl esters, the results varied. In the activated ester **17** (Table 2, entry 13), under standard LiOH conditions, only the alcohol (arising from cleavage of the acetate) or alcohol/carboxylic acid products were obtained. In contrast, upon use of the tin reagent the methyl ester was hydrolyzed selectively in the presence of the secondary acetate. This led to further experimentation with substrates **18** and **19** (Table 2, entries 14 and 15). Compound **19** again underwent selective hydrolysis of the methyl ester in the presence of the primary acetate protecting group, whereas **18** underwent quantitative loss of its acetate protecting groups, without hydrolysis of the methyl ester. These observations can be attributed to the ease with which phenolic acetates are removed, owing to the good leaving-group nature of the phenolic moiety. Further complementing this new methodology is the ease with which the resulting carboxylic acid products are isolated. A general workup procedure involved concentration of the crude reaction mixture and redilution in ethyl acetate. The organic layer was then washed three times with either aqueous $KHSO_4$ (0.01N) or HCl (5%), depending on the acid lability of the substrate. In most cases, this procedure produced a virtually pure sample of the carboxylic acid owing to the high solubility of Me_3SnOH in water[2c,6] (typically ≤ 2 mol% of Me_3SnOH by ^1H NMR spectroscopy). When materials of higher purity were required, the remaining tin reagent could be removed by further aqueous washes or silica gel chromatography.

In a final test to demonstrate the definitive tolerance of epimerization-prone substrates to Me_3SnOH, dichlorinated phenyl glycine derivative **22**[7] (Table 3) was prepared in four steps from commercially available (*R*)-4-hydroxyphenylglycine[8] and (*R*)-Mosher acid chloride under standard conditions (CH_2Cl_2, pyridine, 0→25 °C).[9] ^1H NMR spectroscopic analysis of the resulting coupled product **22** indicated a d.r. of 96:4. The attempted hydrolysis was then carried out under standard LiOH and LiOOH conditions, and with Me_3SnOH and potassium trimethylsilanolate, a reagent reported to promote mild, epimerization-free hydrolysis of amino acid esters.[10] After exposure of the diastereomeric mixture of methyl esters **22** (*R*,*R*/*S*,*R* 96:4) to 1.1 equivalents of LiOH for 20 min at 0 °C, followed by warming to room temperature for 20 min, a mixture of diastereomeric carboxylic acids was obtained in a ratio of 43:57 (*R*,*R*/*S*,*R*) (measured by ^1H NMR spectroscopy), while treatment with LiOOH resulted in decomposition. When the mixture of esters **22** was treated with 1.5 equivalents of $KOSiMe_3$ for 4 h at room temperature, a mixture of carboxylic acids (*R*,*R*/*S*,*R* 20:80) was isolated. However, when **22** was exposed to 3.0 equivalents of Me_3SnOH in 1,2-dichloroethane at 80 °C for 20 min, the corresponding acid was isolated in 98% yield with only slight

Table 3: Methyl ester hydrolysis of chlorinated (*R*)-Mosher amide–(*R*)-4-hydroxyphenylglycine derivatives.[a]



22 96:4 d.r.[b] **22a**

Entry	Substrate	Conditions	Product d.r.
1	**22**	Me_3SnOH (3.0 equiv), 1,2-DCE, 80 °C	94:6
2	**22**	LiOH (1.1 equiv), THF, MeOH, H_2O, 0→25 °C	43:57
3	**22**	$KOSiMe_3$ (1.5 equiv), Et_2O, 25 °C	20:80

[a] Reactions were carried out on a 0.01–0.04-mmol scale. [b] Prepared by reaction of the corresponding amine and acid chloride in the presence of pyridine in dichloromethane at room temperature.

erosion of the stereochemical integrity (*R*,*R*/*S*,*S* 94:6). When the same experiments were carried out with the diastereomer of **22** obtained from the opposite enantiomer of the Mosher acid chloride (*R*,*S*/*S*,*S* 99:1), the results were similar but not identical (conditions of Table 3, entry 1: d.r. = 97:3; conditions of Table 3, entry 2: d.r. = 64:36; conditions of Table 3, entry 3: d.r. = 69:31).

With these final results standing as a powerful testament to the mildness of the presently introduced method, we anticipate its applicability and usefulness in chemical synthesis to be widespread.

Experimental Section

General procedure: The carboxylic ester (0.01–0.15 mmol) was dissolved in 1,2-dichloroethane and after addition of trimethyltin hydroxide (1–10 equiv), the mixture was heated at 60–80 °C until TLC analysis indicated a complete reaction. After completion of the reaction, the mixture was concentrated in vacuo, and the residue was taken up in ethyl acetate (≈15 mL). The organic layer was washed with aqueous $KHSO_4$ (0.01N) or HCl (5%) (3×5–15 mL). The organic layer was then washed with brine (5–15 mL) and dried over sodium sulfate. Removal of the solvent in vacuo afforded the carboxylic acid, often in >98% purity (by ^{1}H NMR spectroscopy).

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Table 4: Selected physical properties for compounds **9a**, **10a**, **14a**, **17a**, and **22a**.

9a: R_f = 0.12 (silica gel, EtOAc/hexanes 1:1); $[\alpha]_D^{32} = -32.5$ (CH_2Cl_2, c = 1.20); IR (film): $\tilde{\nu}_{max}$ = 3323, 3060, 2978, 2931, 1696, 1665, 1519, 1368, 1249, 1166, 1070, 737 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.56–7.54 (m, 2H), 7.26–7.25 (m, 3H), 7.09 (br d, J = 7.4 Hz, 1H), 4.89 (m, 2H), 3.48 (dd, J = 13.1, 4.4 Hz, 1H), 3.34 (m, 1H), 1.46 (br s, 9H), 1.25 ppm (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.4, 172.9, 133.2, 129.4, 129.2, 127.4, 53.1, 50.0, 29.6, 29.2, 28.3, 18.1 ppm; HRMS (ESI-TOF): calcd for $C_{17}H_{24}N_2O_5SeNa^+$ [M+Na]$^+$: 439.0743; found: 439.0743

10a: R_f = 0.10 (silica gel, EtOAc/hexanes 1:1); IR (film): $\tilde{\nu}_{max}$ = 3406, 2917, 1629, 1527, 1352, 1095, 1038, 718 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD): δ = 8.03–7.99 (m, 2H), 7.51–7.48 (m, 1H), 6.89 (s, 1H), 6.22 ppm (s, 1H); ^{13}C NMR (150 MHz, CD_3OD): δ = 194.6, 171.0, 152.0, 144.3, 138.9, 135.4, 134.7, 131.8, 127.2, 124.8 ppm; HRMS (ESI-TOF): calcd for $C_{10}H_6BrNO_5H^-$ [M−H]$^-$: 297.9357; found: 297.9354

14a: R_f = 0.30 (silica gel, EtOAc/hexanes 7:3); IR (film): $\tilde{\nu}_{max}$ = 3460, 2980, 2934, 2859, 1731, 1714, 1467, 1374, 1181, 1109 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.00 (septet, J = 6.2 Hz, 1H), 2.37–2.24 (m, 4H), 1.65–1.60 (m, 4H), 1.36–1.33 (m, 4H), 1.22 ppm (d, J = 6.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.3, 67.4, 34.5, 28.6, 28.6, 24.7, 24.7, 24.6, 21.7 ppm; HRMS (ESI-TOF): calcd for $C_{11}H_{20}O_4Na^+$ [M+Na]$^+$: 239.1254; found: 239.1255

17a: Inseparable mixture of ≈1:1 diastereomers: R_f = 0.34 (silica gel, EtOAc/hexanes 7:3); $[\alpha]_D^{32} = -22.3$ (CH_2Cl_2, c = 0.60); IR (film): $\tilde{\nu}_{max}$ = 3380, 2925, 2854, 1737, 1719, 1460, 1375, 1252, 1094, 836 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.37 (s, 2×1H), 6.05 (m, 2×1H), 5.06–5.03 (m, 2×1H), 2.94–2.84 (m, 2×1H), 2.79–2.74 (m, 2×1H), 2.69–2.65 (m, 2×1H), 2.14 (s, 2×3H), 2.10–2.02 (m, 2×2H), 1.95 (m, 2×1H), 1.39 (d, J = 6.12 Hz, 3H), 1.36 (d, J = 6.18 Hz, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H), 0.00 (s, 3H), −0.02 ppm (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 178.3, 170.6, 157.8, 152.4, 144.5, 134.0, 120.2, 70.3, 66.6, 66.5, 32.1, 29.9, 25.9, 25.9, 25.2, 25.0, 22.9, 21.5, 18.1, −4.6, −4.6, −4.7 ppm; HRMS (ESI-TOF): calcd for $C_{20}H_{31}NO_5SiH^+$ [M+H]$^+$: 394.2044; found: 394.2049

22a: R_f = 0.34 (silica gel, MeOH/CH_2Cl_2 1:9); $[\alpha]_D^{32} = -62.6$ (MeOH, c = 0.67); IR (film): $\tilde{\nu}_{max}$ = 3381, 2920, 2856, 1732, 1649, 1454, 1270, 1164, 1106 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD): δ = 7.59–7.57 (m, 2H), 7.45–7.44 (m, 5H), 5.48 (br s, 1H), 3.88 (s, 3H), 3.40 ppm (m, 3H); ^{13}C NMR (150 MHz, CD_3OD): δ = 168.1, 153.4, 137.0, 133.7, 131.0, 130.5, 129.8, 129.5, 129.4, 126.5, 124.6, 61.3, 56.1, 55.7, 30.9 ppm; HRMS (ESI-TOF): calcd for $C_{19}H_{16}Cl_2F_3NO_5H^+$ [M+H]$^+$: 466.0430; found: 466.0429

(*R*,*S*)-**22a**: R_f = 0.34 (silica gel, MeOH/CH_2Cl_2 1:9); $[\alpha]_D^{32} = -34.1$ (MeOH, c = 0.27); IR (film): $\tilde{\nu}_{max}$ = 3377, 2917, 2851, 1730, 1694, 1479, 1268, 1166, 1105 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD): δ = 7.46–7.44 (m, 2H), 7.41–7.37 (m, 3H), 7.29 (s, 2H), 5.52 (br s, 1H), 3.85 (s, 3H), 3.62 ppm (m, 3H); ^{13}C NMR (150 MHz, CD_3OD): δ = 168.1, 153.5, 136.3, 134.6, 130.9, 130.4, 129.6, 129.5, 128.5, 126.2, 124.3, 61.3, 56.6, 56.1, 30.9 ppm; HRMS (ESI-TOF): calcd for $C_{19}H_{16}Cl_2F_3NO_5Na^+$ [M+Na]$^+$: 488.025; found: 488.0246

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