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Dimethylaluminum methyltellurate, a new reagent for the cleavage of hindered methyl esters under exceptionally mild conditions by a novel mechanism

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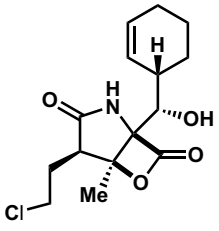
Abstract—An efficient and effective new reagent $(Me_2AlTeMe)_2$ has been developed for the conversion of methyl esters to the corresponding carboxylic acids in toluene solution at 23 °C.

In the course of recent investigations on the total synthesis of the potent proteasome inhibitor salinosporamide A (**1**)[1] and related structures we encountered great difficulty in the hydrolysis of the hindered methyl ester function in a late intermediate (**2**).[2,3] Because of the combination of strong steric shielding of the COOMe carbonyl in **2** and the ease of decomposition by retroaldol pathways, the conversion of methyl ester **2**, for example, R = *i*-Pr, into the corresponding carboxylic acid failed completely under a wide variety of acidic and basic conditions.[4] In addition, various reagents that might function to cleave the O–CH_3 bond of COOMe in **2** by S_N2 displacement (e.g., *n*-PrSLi or C_6H_5SLi in DMF or HMPA) also did not lead to the desired acid. As a result we turned our attention to the use of novel mixed-function reagents, that is, combining Lewis acidic and nucleophilic centers, as a new type of reactant that might activate the COOMe group by coordination and also effect nucleophilic attack on the methyl group of the activated species. It was with the guidance of this idea that we have discovered a very effective new reagent, dimethylaluminum methyltellurate $(Me_2AlTeMe)_2$.



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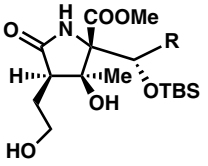

2

Dimethylaluminum methyltellurate is readily prepared by heating tellurium powder (1.2 equiv) and trimethylaluminum (1 equiv) in toluene (Aldrich Co.) at reflux under nitrogen for 6 h and cooling to room temperature.[5–7] It can be obtained as a colorless solid (very air sensitive) upon evaporation of toluene in vacuo. CAUTION: Because of their unpleasant odor, organotellurium reagents should be prepared and used only in a well-ventilated hood; treatment of $(Me_2AlTeMe)_2$ with either bleach (aq NaOCl) or 1 N hydrochloric acid effects its destruction and deodorization. The colorless solutions of $(Me_2AlTeMe)_2$ thus obtained (0.8 M) were stable under a nitrogen atmosphere at room temperature for at least 1 week. This toluene solution of $(Me_2AlTeMe)_2$ was remarkably effective for the required conversion of RCOOMe to RCOOH even at ambient temperature (23 °C in our experiments). Table 1 shows eight examples of such cleavage reactions of hindered methyl esters at 23 °C for reaction times in the range of 6–24 h. In each case the reactions were clean and gave good yields of solated pure products. In entry 1, the *N*-benzyl group and γ-lactam function of methyl *N*-benzylpyroglutamate were unaffected and, in addition, no racemization occurred. Methyl mesitoate, a highly hindered methyl ester, was readily cleaved (entry 2). The corresponding benzyl and allyl esters (entries 3 and 4) were also cleaved, but somewhat more slowly. The intermediates shown in

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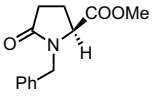
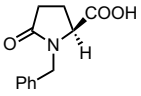
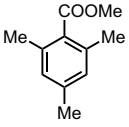
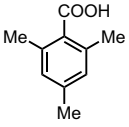
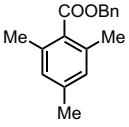
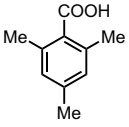
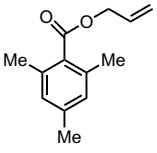
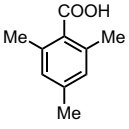
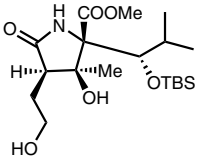
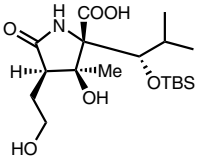
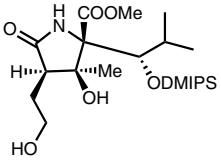
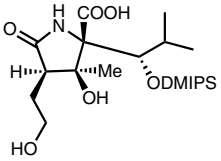
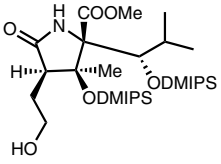
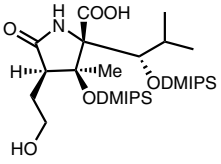
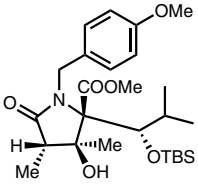
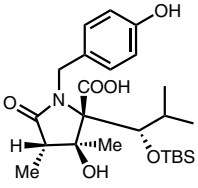
Table 1. $(Me_2AlTeMe)_2$ promoted conversion of esters into carboxylic acids in toluene at 23 °C

Entry	Ester	Acid[a]	$Me_2AlTeMe$ (equiv)	Time (h)	Isolated yield (%)
1			3.2	6	91
2			1.2	6	91
3			1.2	14	87
4			1.2	12	89
5			5.2	12	81
6			5.2	12	83
7			5.2	12	79
8			5.2	24	80

[a] All products were characterized by ^1H NMR, IR, and mass spectroscopy.

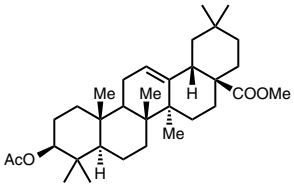
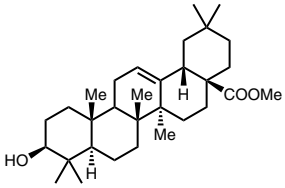
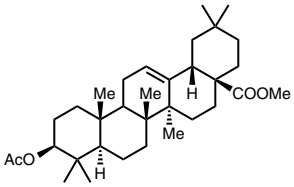
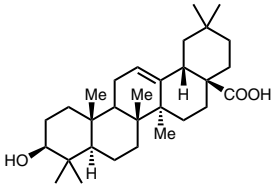
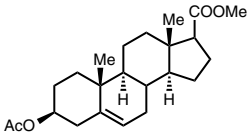
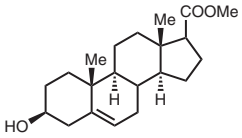
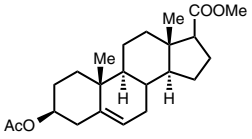
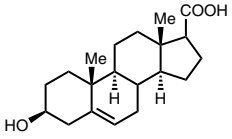
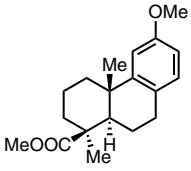
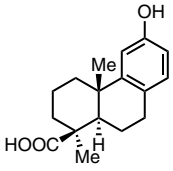
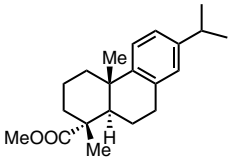
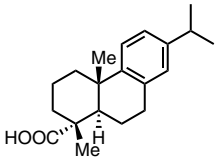
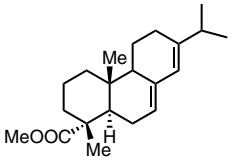
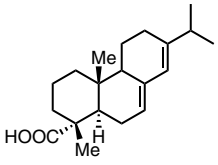
entries 5–7 for the synthesis of salinosporamide analogs were likewise cleaved cleanly in good yields. In these cases it should be noted that the *t*-butyldimethylsilyl (TBS) and dimethylisopropylsilyl (DMIPS) protecting groups were not removed. However, it was necessary to use a larger excess of the tellurium reagent because of the presence of reactive OH and NH groups. The example shown in entry 8 of Table 1 shows that $(Me_2AlTeMe)_2$ is capable of cleaving aromatic methyl ethers as well as methyl esters under mild conditions. The rate of ArO–Me scission is somewhat slower than that for RCOOMe. Because of the observed effectiveness of $(Me_2AlTeMe)_2$ in the demethylation of very hindered esters, we believe that nucleophilic attack by tellurium on methyl to displace $RCOOAlMe_2$ best accounts for the cleavage reaction, as shown.

$$RCOOMe + (Me_2AlTeMe)_2 \rightarrow RCOOAlMe_2 + MeTeMe$$

It is noteworthy that the analogous reagents $(Me_2AlSMe)_2$[5] and $(Me_2AlSeMe)_2$[6] were found to be relatively ineffective for methyl ester cleavage.

Because volatile organotellurium compounds have a characteristic and unpleasant odor, it was important to devise an isolation procedure that avoids this problem and also possible toxicity issues. Fortunately, it was found that simply by stirring the reaction mixture with 2 N hydrochloric acid for ca. 2 h at 23 °C after dilution with ethyl acetate the organotellurium coproducts were converted to odorless water-soluble form. This reaction process and product isolation are illustrated by the experimental procedure for the conversion of methyl

Table 2. $(Me_2AlTeMe)_2$ promoted conversion of esters into carboxylic acids in toluene at 23 °C

Entry	Ester	Acid[a]	$Me_2AlTeMe$ (equiv)	Time (h)	Isolated yield (%)
1			2.2	8	85
2			3.2	10	80[b]
3			2.2	6	95
4			3.2	8	89[b]
5			3.2	14	90
6			2.2	10	88
7			2.2	8	85

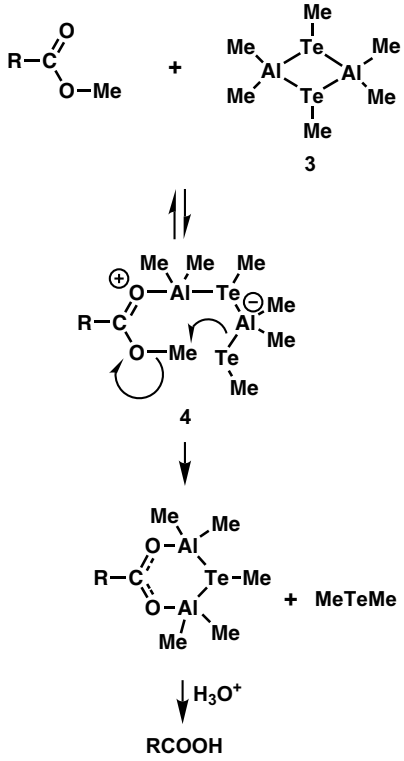
[a] All products were characterized by ^1H NMR, IR, and mass spectroscopy.
[b] Reaction was carried out at 50 °C.

mesitoate to mesitoic acid (Table 1, entry 2).[8] It should be added that volatile organotellurium coproducts such as Me_2Te (bp 93 °C) can also be removed from the reaction mixture by distillation of solvent and byproducts under reduced pressure into a cold trap, the contents of which are then treated with aqueous bleach to destroy the odor of Te compounds.

Additional examples of dimethylaluminum methyltellurate induced Me–O cleavage with even more hindered ester substrates are summarized in Table 2. Methyl acetyloleanolate undergoes deacetylation followed by somewhat slower demethylation to give either methyl oleanolate (Table 2, entry 1) or oleanolic acid (Table 2, entry 2), depending on the amount of reagent used and the reaction time. Similar results were obtained with the steroidal acetoxy methyl ester shown in entries 3 and 4 of Table 2. Methyl podocarpate *O*-methyl ether, an extremely hindered methyl ester (Table 2, entry 5) underwent cleavage of both the ester and ether methoxy groups to afford podocarpic acid in high yield. Finally, methyl dehydroabietate (entry 6) and methyl abietate (entry 7) were converted cleanly to the corresponding acids. The mildness of the conditions for the successful demethylation of the very hindered methyl esters shown in Table 2 provides ample evidence of the potency and potential of the new demethylating reagent.

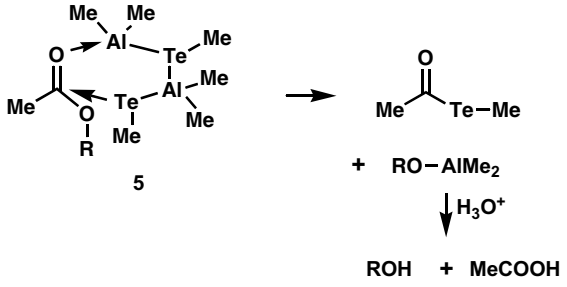
Although the structure of dimethylaluminum methyl tellurate has not been determined it is likely to be the

bridged dimeric species **3** on the basis of much analogy[9] and especially because the closely related sulfur analog $(Me_2AlSMe)_2$ has been determined to be this type of S-bridged dimer.[10] On the basis of this structure a most intriguing possibility emerges for the mechanism of the mild and efficient cleavage of methyl esters by the new reagent **3**. This mechanistic pathway is summarized in Scheme 1. In this pathway the methyl ester is activated by coordination of the COOMe carbonyl oxygen to an aluminum of **3** leading after cleavage of one of the Al–Te bridge bonds to the putative intermediate **4**. Cleavage of the Me–O bond in **4** could then occur by an unusual intramolecular backside displacement on methyl by the distal TeMe subunit, as shown. Because of the number of bonds in the path between the methyl group being attacked and the terminal Te nucleophile and the length of the bonds to Te, a stereoelectronically favorable colinear O–Me–Te–Me transition state is available from **4**.[11] This would represent an extremely rare and singular example of an intramolecular backside nucleophilic displacement reaction in which the nucleophile is linked to the leaving group. Of course, it is also possible that a two-step decomposition pathway occurs from **4**: terminal MeTe–Al bond dissociation to form $MeTe^-$ which then attacks the methyl ester Me group as an external nucleophile to produce the ester cleavage product. Whichever of these two alternatives operates, it is clear that the mechanistic pathway shown in Scheme 1 provides a simple explanation of the unique reactivity of the reagent **3** with hindered carboxylic acid methyl esters. It is also apparent that the process of methyl ester cleavage outlined in Scheme 1 represents a new paradigm for ester deprotection.



Scheme 1. Possible mechanistic pathway for the facile Me–O bond cleavage of methyl esters by **3**.

A similar explanation can be used for the cleavage of aromatic methyl ethers by **3**, except that in this case the two-step pathway for Me–O bond cleavage from the complex corresponding to **4** becomes much more likely for stereoelectronic reasons. Finally, the deacetylation reactions induced by the reagent **3** (Table 2, entries 1–4) can be explained by attack on the acetate carbonyl of complex **5** by the distal MeTe group.



References and notes

1. Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 355–357.
2. Reddy, L. R.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230–6231.
3. Reddy, L. R.; Fournier, J.-F.; Reddy, B. V. S.; Corey, E. J. *J. Am. Chem. Soc.*, submitted for publication.
4. For example, none of the carboxylic acid corresponding to **2** could be obtained using sodium, lithium, barium, or lanthanum hydroxides using a variety of solvents and temperatures. Aqueous acids and Lewis acidic conditions (e.g., BCl_3, Me_3LiI) also failed. For reviews on methyl ester cleavage, see: (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999; (b) Kocienski, P. J. *Protecting Groups*, 3rd ed.; George Thieme: Stuttgart, New York, 2004; (c) Salomon, C. J.; Mata, E. G.; Mascaretti, O. A. *Tetrahedron* **1993**, *49*, 3691–3734; (d) Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1378–1382; (e) Olah, G. A.; Narang, S. C.; Salem, G. F.; Gupta, B. G. B. *Synthesis* **1981**, 142–143; (f) Marchand, P. S. *J. Chem. Soc., Chem. Commun.* **1971**, 667–668; (g) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* **1970**, 4459–4462.
5. For the analogous sulfur reagent, see: (a) Corey, E. J.; Kozikowski, A. P. *Tetrahedron Lett.* **1975**, 925–928; (b) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 5829–5830; (c) Hatch, R. P.; Weinreb, S. M. *J. Org. Chem.* **1977**, *42*, 3960–3961.
6. For the corresponding selenium reagent, $Me_2AlSeMe$, prepared by reaction of selenium with Me_3Al, see: Kozikowski, A. P.; Ames, A. *J. Org. Chem.* **1978**, *43*, 2735–2737.
7. At the end of the 6 h reaction time all the gray-white Te powder had dissolved and only a small amount of an insoluble colorless solid remained at the bottom of the flask (possibly due to the presence of impurity in the Te powder used). The clear supernatant solution of Me_2Al-TeMe was then drawn off by syringe as needed.
8. A solution of methyl mesitoate (1.78 g, 10 mmol) in a 2 mL of toluene was added to a stirred solution of freshly prepared dimethylaluminum methyltellurolate (**3**, 15 mL; 12 mmol; 0.8 M solution) in toluene. The mixture was

stirred at room temperature for 6 h, after which the reaction was complete as indicated by TLC analysis. The reaction mixture was treated with 2 N HCl (50 mL) and ethyl acetate (50 mL) and the resulting mixture was stirred vigorously at room temperature for 2 h. The organic phase was separated and the aqueous phase was twice extracted with ethyl acetate (2×30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo, purified by column chromatography on silica gel using ethyl acetate–hexane (1:9) to afford 1.50 g (91.5%) of pure mesitoic acid as a colorless solid, mp 153–155 °C (lit. mp 154–155 °C).

9. See: (a) Cowley, A. H.; Jones, R. H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1143–1145; (b) Eisch, J. J. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Eds.; Pergamon: Oxford, UK, 1982; Vol. 1, pp 557–622.
10. Haaland, A.; Stokkeland, O.; Weidlein, J. *J. Organomet. Chem.* **1975**, *94*, 353–360.
11. The large difference between **3** $(Me_2AlSMe)_2$ and $(Me_2Al-SeMe)_2$, which at first seems surprising, may be due to the shorter Al–S and Al–Se bond lengths and different bond angles, which do not provide the most favorable geometry for intramolecular nucleophilic attack on the O–CH_3 group in complex analogous to **4**.