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Mild and Efficient Lewis Acid-Promoted Detritylation in the Synthesis of *N*-Hydroxy Amides: A Concise Synthesis of (−)-Cobactin T

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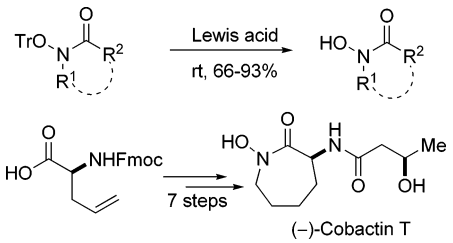


An efficient, high-yielding Lewis acid promoted deprotection of *O*-trityl hydroxylamine derivatives is described. A range of acid-labile protecting groups, such as *N*-Boc and *O*-TBS, were tolerated under these mild conditions. The present method is applicable to the synthesis of a broad range of hydroxylamine derivatives, including *N*-hydroxy amides (hydroxamic acids), *N*-hydroxy sulfonamides, and *N*-hydroxy ureas, which often exhibit significant biological activities. An application of this methodology for a concise synthesis of (−)-Cobactin T (**18**) is also demonstrated.

Hydroxamic acid is one of the reoccurring motifs in the structure of metalloproteinase inhibitors, including matrix metalloproteinase (MMP),[1] neutral endopeptidase (NEP),[2] and human histone deacetylase (HDAC). Although the trityl group (Tr) has been widely used as a protecting group for the hydroxyl group,[3] few reports have appeared wherein a trityl group was used as a protecting group in the synthesis of hydroxamic acids.[4] In those cases, trifluoroacetic acid (TFA) was commonly used as the deprotecting reagent. By taking advantage of potential bidentate chelation of the hydroxamate unit, a Lewis acid (LA) could potentially facilitate the removal of the trityl group through the coordinated intermediate **A** (Scheme 1). Herein, we report a mild and efficient Lewis acid-mediated deprotection of trityl group in the synthesis of *N*-hydroxylamine derivatives.[5]

SCHEME 1

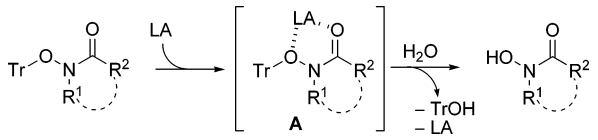
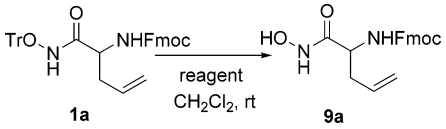


TABLE 1. Deprotection of *O*-Trityl Hydroxamic Acid 1a[a]



		9a (yield, %)/**1a** (conversion, %)[b]		
entry	reagent (equiv)	10 min	30 min	1 h
1	$ZnBr_2$ (10)	79/82	60/87	55/89
2	$ZnBr_2$ (5)	60/68	72/82	77/85
3	$ZnCl_2$ (5)	35/39	38/45	39/45
4	$Zn(OTf)_2$ (5)	0/0	2/3	3/5
5	$MgBr_2$ (10)	75/84	91/94	84/96
6	$MgBr_2$ (5)	72/82	80/93	83/96
7	BF_3•OEt_2 (2)	68/83	67/84	66/85
8[c]	BF_3•OEt_2 (2)	88/89	94/98	–
9[d,e]	Amberlyst 15	<10/12	14/21	25/30

[a] All reactions were performed on a 0.05 mmol scale in CH_2Cl_2 (1 mL) at room temperature unless otherwise specified. [b] Percentages of **9a** formed and **1a** that remained were determined by HPLC analysis relative to an internal standard, 4-bromobiphenyl. [c] MeOH/CH_2Cl_2 (0.5 mL/0.5 mL) as the solvent was employed. [d] Amberlyst 15 ion-exchange resin (60 mg) and MeOH/CH_2Cl_2 (1 mL/1 mL) as the solvent were employed. [e] **9a** (yield)/**1a** (conversion) was 57/58, 80/81, and 85/87 at 3, 6, and 8 h, respectively.

To test the feasibility of the detritylation process, compound **1a** was initially selected and examined under various Lewis acid conditions (Table 1). Attention was mainly focused on the use of mild Lewis acid conditions. The yield of **9** and the percent conversion of **1a** were determined by HPLC analysis using 4-bromobiphenyl as an internal standard. Upon treatment of **1a** with 10 equiv of $ZnBr_2$ in CH_2Cl_2, the detritylation took place rapidly to reach over 80% conversion within 10 min at ambient temperature.[6] However, the yield of the desired product **9a** decreased to 55% after 1 h stirring, presumably due to decomposition in the presence of excess Lewis acid (entry 1). Reducing the amount of $ZnBr_2$ (5 equiv) gave a comparable result without diminution of **9a** (entry 2). As previously reported, both $ZnCl_2$ and $ZnBr_2$ exhibited equal efficiency in the detritylation of trityl-protected hydroxyl compounds.[6a] By using $ZnCl_2$ in this *O*-trityl hydroxamate example, however, the detritylation proceeded to a significantly lesser extent (entry 3). $Zn(OTf)_2$ was found to be totally ineffective (entry 4). Additionally, $MgBr_2$ has been employed to remove the trityl group

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(1) Representative reviews, see: (a) Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. H. *Chem. Rev.* **1999**, *99*, 2735. (b) Matter, H.; Schudok, M. *Curr. Opin. Drug Discovery Dev.* **2004**, *7*, 513, and the references cited therein.

(2) Walz, A. J.; Miller, M. J. *Org. Lett.* **2002**, *4*, 2047, and the references cited therein.

(3) Green, T. W.; Wuts, P. G. M. *Protecting Group in Organic Synthesis*; John Wiley & Sons: New York, 1999; pp 102−104.

(4) (a) Hanessian, S.; Moitessier, N.; Wilmouth, S. *Tetrahedron* **2000**, *56*, 7643. (b) Hanessian, S.; Moitessier, N.; Gauchet, C.; Vian, M. *J. Med. Chem.* **2001**, *44*, 3066. (c) Wittich, S.; Scherf, H.; Xie, C.; Brosch, G.; Loidl, P.; Gerhäuser, C.; Jung, M. *J. Med. Chem.* **2002**, *45*, 3296. (d) Remiszewski, S. W.; Sambucetti, L. C.; Bair, K. W.; Bontempo, J.; Cesarz, D. *J. Med. Chem.* **2003**, *46*, 4609.

(5) To the best of our knowledge, except TFA, other conditions for detritylation in the synthesis of hydroxamates, *N*-hydroxyl sulfonamide, and *N*-hydroxyamine derivatives have not been investigated yet.

(6) (a) Kohli, V.; Blöcker, H.; Köster, H. *Tetrahedron Lett.* **1980**, *21*, 2683. (b) Lampe, T. F.; Hofmann, H. M. R. *Tetrahedron Lett.* **1996**, *37*, 7695.

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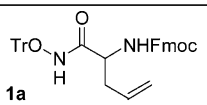
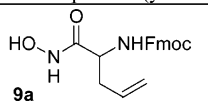
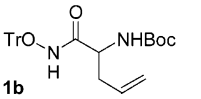
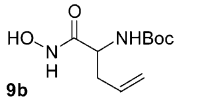
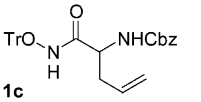
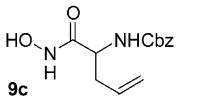
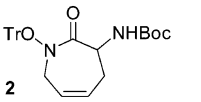
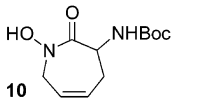
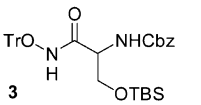
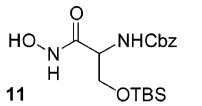
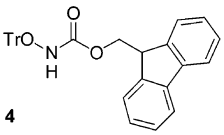
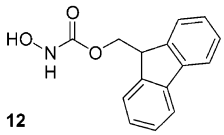
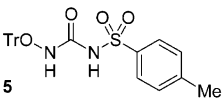
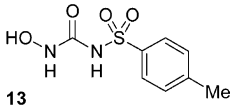
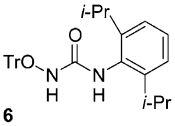
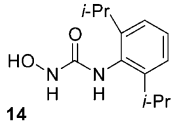
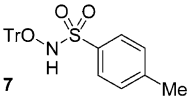
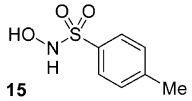
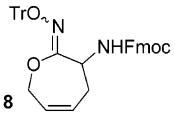
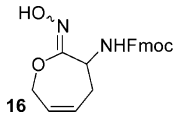
TABLE 2. Lewis Acid Promoted Detritylation of *O*-Trityl Hydroxlamine Derivatives[a]

entry		substrate	reagent	time (min)	product (yield/%)[b]
1	**1a**	 **1a**	$MgBr_2$	40	 **9a** (86)
2	**1a**		$BF_3{\cdot}OEt_2$	15	**9a** (89)
3[c]	**1a**		Amberlyst® 15	6 h	**9a** (82)
4	**1b**	 **1b**	$MgBr_2$	25	 **9b** (70)
5[d]	**1b**		$BF_3{\cdot}OEt_2$	10	**9b** (76)
6[e,f]	**1b**		TFA	60	**9b** (30)
7	**1c**	 **1c**	$MgBr_2$	60	 **9c** (81)
8	**2**	 **2**	$MgBr_2$	10	 **10** (66)
9[d]	**2**		$BF_3{\cdot}OEt_2$	10	**10** (74)
10[e,f]	**2**		TFA	60	**10** (28)
11	**3**	 **3**	$MgBr_2$	15	 **11** (79)
12	**4**	 **4**	$MgBr_2$	3 h	 **12** (89)
13[g]	**4**		$BF_3{\cdot}OEt_2$	45	**12** (93)
14	**5**	 **5**	$MgBr_2$	45	 **13** (85)
15	**5**		$BF_3{\cdot}OEt_2$	45	**13** (83)
16	**6**	 **6**	$MgBr_2$	6 h	 **14** (92)
17[g]	**6**		$BF_3{\cdot}OEt_2$	8 h	**14** (85)
18	**7**	 **7**	$BF_3{\cdot}OEt_2$	4 h	 **15** (80)
19[h]	**7**		$ZnBr_2$	36 h	**15** (63)
20[i]	**8**	 **8**	$ZnBr_2$	10	 **16** (82)

[a] All reactions were performed on a 1.0−2.0 mmol scale with $MgBr_2$ (5.0 equiv) in CH_2Cl_2, or $BF_3{\cdot}OEt_2$ (2.0 equiv) in MeOH/CH_2Cl_2 (1/1) at room temperature unless otherwise specified. [b] Isolated yield. [c] Amberlyst 15 ion-exchange resin (1.0 g/mmol) in MeOH/CH_2Cl_2 (1/1) was employed. [d] MeOH/CH_2Cl_2 (1/4) was employed. [e] 5% TFA/CH_2Cl_2 was employed. [f] **1b** (5%) or **2** (8%) was recovered. [g] MeOH/$CHCl_3$ (1/4) was employed. [h] $ZnBr_2$ (5.0 equiv) in MeOH/CH_2Cl_2 (1/1) was employed. [i] $ZnBr_2$ (10.0 equiv) in CH_2Cl_2 was employed.

from 1-*O*-Benzyl-3-*O*-tritylglycerol to give 1-*O*-benzylglycerol.[7] In that report, the deprotection required 24 h in refluxing benzene to reach completion or 6 days with 90% conversion at room temperature. Upon treatment of **1a** with $MgBr_2$ (10 equiv), surprisingly, the cleavage of trityl group went to completion within 30 min at ambient temperature (entry 5). In fact, 5 equiv of $MgBr_2$ was sufficient to achieve high conversion with excellent yield within 1 h (entry 6). These results suggest that the bi-dentate coordination of the hydroxamate moiety with Mg^{2+} accelerate the cleavage of the trityl group. The use of $BF_3{\cdot}OEt_2$ (2 equiv) in dichloromethane was next examined.[8] Under this condition, only a moderate yield of **9a** was detected (entry 7). By using methanol as the cosolvent, the detritylation proceeded cleanly within 10 min and a higher yield was observed (entry 8). Finally, the heterogeneous removal of the trityl group using Amberlyst 15 ion-exchange resin proceeded slowly, but smoothly, to reach completion at approximately 10 h (entry 9).[9]

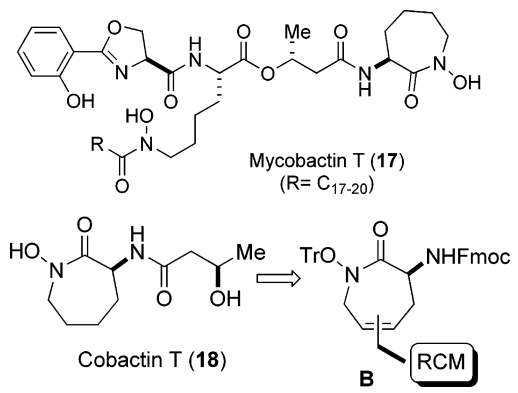
With these practical detritylation conditions in hand, we turned our attention to expanding the scope of this process. A variety of chemotypes with different functionalities were studied under optimized conditions, namely $MgBr_2$ (5 equiv) in CH_2Cl_2 or $BF_3{\cdot}OEt_2$ (2.0 equiv) in CH_2Cl_2/MeOH at room temperature (Table 2). The deprotection of **1a** with $MgBr_2$ or $BF_3{\cdot}OEt_2$ proceeded as expected, completing within 40 min to provide **9a** in 86 and 89% isolated yield, respectively (entries 1−2). The use of Amberlyst 15 ion-exchange resin provided a viable alternative to **9a** (82%, entry 3). A range of functional groups such as *O*-TBS, *N*-Cbz, and especially *N*-Boc were well tolerated under $MgBr_2$ and $BF_3{\cdot}OEt_2$ conditions with good

(7) Haraldsson, G. G.; Stefansson, T.; Snorrason, H. *Acta Chim. Scand.* **1998**, *52*, 824.

(8) Cabaret, D.; Wakselman, M. *Can. J. Chem.* **1990**, *68*, 2253.

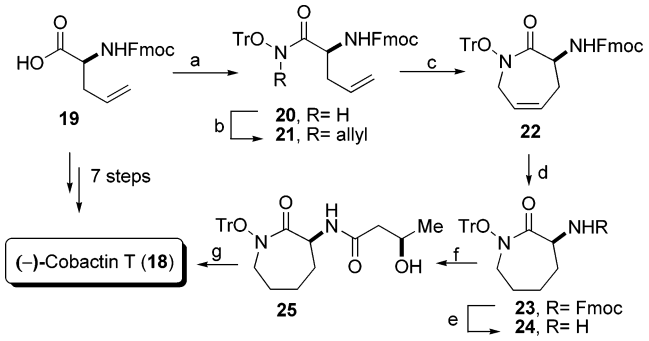
(9) Malanga, C. *Chem. Ind. (London)* **1987**, 856.

CHART 1. Representative Nature Products Containing Hydroxamic Acid Unit



isolated yields (66−81%, entries 4−5 and 7−9).[10] In a comparison between substrates **1b** and **2**, both cyclic and acyclic trityl-protected hydroxamates exhibited similar reactivity. The success of selective cleavage of the trityl group in the presence of *N*-Boc demonstrates the efficiency of this coordinative detritylation process. Not surprisingly, *N*-Boc did not survive under trifluoroacetic acid (TFA) condition. Even under 5% TFA/CH_2Cl_2 solution, both **1b** and **2** gave desired product in low yields (ca. 28−30%, entries 6 and 10) with low recovery of starting material. These results may be attributed to the simultaneous loss of the Boc group during detritylation process. The methodology can be further expanded to incorporate other *N*-hydroxylamine derivatives, such as *N*-hydroxy carbamate (**12**), *N*-hydroxy ureas (**13**−**14**), and *N*-hydroxy sulfonamide (**15**).[11] The efficiency of detritylation seems to depend on the nature of hydroxamate unit and Lewis acid employed. For example, the reaction of *O*-trityl *N*-hydroxy carbamate **(4)** reacted more rapidly with $BF_3{\cdot}OEt_2$ than with $MgBr_2$, although both afforded **12** in excellent yields (entries 12−13). In the case of an urea-sulfonamide-hybrid hydroxamate (**5**), the removal of trityl group occurred with equal efficiencies and yields under both Lewis acid conditions (entries 14−15). The detritylation of **6**[11a] and **7** took place at a relatively slower rate than compounds **1**−**5** as described above (entry 16−18). In addition, $MgBr_2$ did not cleave the trityl group from *O*-trityl *N*-hydroxy sulfonamide **7**. The trityl group of **7** could be successfully removed, but to a lesser extent under $ZnBr_2$ (5.0 equiv) conditions using methanol as a cosolvent (entry 19). Finally, an oxime-containing hydroxylamine derivative **8** was examined under several conditions described above. This oxime moiety was extremely sensitive to acidic conditions such as TFA, HCl, and Amberlyst 15 ion-exchange resin. It was also unstable under a diverse set of Lewis acids including $AlCl_3$, $MgBr_2$, and $BF_3{\cdot}OEt_2$, presumably due to rapid hydrolysis of the oxime unit under these conditions. Gratifyingly, the desired product **16** was obtained in 82% isolated yield (entry 20) by using 10 equiv of $ZnBr_2$ in CH_2Cl_2 within 10 min. In most cases, the desired product in an analytically pure form could be easily obtained by recrystallization or precipitation from the crude mixture.

SCHEME 2. Synthesis of (−)-Cobactin T (18)[a]



[a] **Reagents and Conditions:** (a) EDC, HOBt, *N*-methylmorpholine, $TrONH_2$, CH_2Cl_2, rt, 2 h, 89%; (b) Allyl methyl carbonate, $Pd(PPh_3)_4$ (0.02 equiv), MeCN, 45 min, 86%; (c) Grubbs II catalyst (0.05 equiv), CH_2Cl_2, 40 °C, 3 h, 85%; (d) H_2 (15 psi), 5 wt % Pt/C (0.05 equiv of Pt), EtOAc, rt, 1.5 h; (e) Et_3N, MeCN, rt, 12 h, 68% (two steps); (f) (*R*)-3-hydroxybutyric acid, EDC, HOAt, *N*-methylmorpholine, $CHCl_3$, rt, 1 h, 70%; (g) $BF_3{\cdot}OEt_2$, CH_2Cl_2/MeOH (4/1, 0.1 M), rt, 5 min, 45%; or (h) Amberlyst 15 ion-exchange resin, CH_2Cl_2/MeOH (1/4), rt, 2 h, 80%.

To further demonstrate the versatility and effectiveness of this process, we applied the detritylation methodology to a novel synthesis of (−)-Cobactin T (**18**). Mycobactin T (**17**) and Cobactin T are the siderphore growth promoters isolated from mycobacteria. Both macromolecules contain a novel cyclic hydroxamate unit (Chart 1).[12] The importance of mycobactin family in the aspect of drug resistance in strains of tuberculosis has stimulated a significant level of effort in synthesis of diverse analogs relative to natural mycobactins. Among them, Cobactin T, one of the major fragments of Mycobactin T, had been previously synthesized.[12,13] These reports feature intramolecular lactam formation or Mitsunobu type cyclization to construct the novel *N*-hydroxy lactam ring. In our retrosynthetic analysis, we envisioned that the ring closing metathesis (RCM) would provide the key lactam ring (**B**) in a highly efficient way. For further installation of the amide side chain, the Fmoc was chosen as the protecting group for the α-amino moiety since it could be easily removed under basic conditions without affecting the acid-labile trityl group.

The synthesis of **18** began with the commercially available *N*-Fmoc L-allylglycine **19** (Scheme 2). The coupling of **19** with $TrONH_2$ using 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBt) as the coupling reagents and *N*-methylmorpholine as the base gave **20** in 89% yield. Under this condition, only a trace amount of de-Fmoc product was observed by HPLC analysis instead of ca. 10% of de-Fmoc product when 4-dimethylaminopyridine

(10) *N*-Boc can be removed under $ZnBr_2$ conditions, see: (a) Kaul, R.; Brouillette, Y.; Sajjadi, Z.; Hansford, K. A.; Lubell, W. D. *J. Org. Chem.* **2004**, *69*, 6131. (b) Nigam, S. C.; Mann, A.; Taddei, M.; Wermuth, C.-G. *Synth. Commun.* **1989**, *19*, 3139. One Boc group of $N(Boc)_2$ can be removed using $MgBr_2$, see: (c) Burkhart, F.; Hoffmann, M.; Kessler, H. *Angew. Chem., Int. Ed.* **1997**, *36*, 1191. Deprotection of *N*-Boc using $BF_3{\cdot}OEt_2$ has been reported, see: (d) Evans, E. F.; Lewis, N. J.; Kapfer, I.; Macdonald, G.; Taylor, R. J. K. *Synth. Commun.* **1997**, *27*, 1819.

(11) Compound **6** has been reported as a potent acyl-CoA cholesterol acyltransferase (ACAT) inhibitor, see (a) Trivedi, B. K.; Holmes, A.; Purchase, T. S.; Essenburg, A. D.; Hamelehle, K. L.; Krause, B. R.; Hes, M. S.; Stanfield, R. L. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2229. *N*-Hydroxy sulfonamides, such as **15**, are potent carbonic anhydrase (CA) inhibitors, see: (b) Scozzafava, A.; Supuran, C. T. *J. Med. Chem.* **2000**, *43*, 3677. (c) Mincione, F.; Menabuoni, L.; Briganti, F.; Mincione, G.; Scozzafava, A.; Supuran, C. T. *J. Enzyme Inhib.* **1998**, *13*, 267.

(12) (a) Hu, J.; Miller, M. J. *J. Am. Chem. Soc.* **1997**, *119*, 3462. (b) Xu, Y.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 4314.

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(14) The *N*-allylation of *O*-benzyl hydroxamate moiety was predominated when the reactive allylating reagent, such as allyl bromide, was employed, see: Johnson, J. E.; Springfield, J. R.; Hwang, J. S.; Hayes, L. J.; Cunningham, W. C.; McClaugherty, D. L. *J. Org. Chem.* **1971**, *36*, 284.

(DMAP) or triethylamine was used as the base. Attempts made to introduce the allyl group onto the nitrogen atom selectively under basic allylation conditions proved to be problematic. Several combinations of bases (K_2CO_3 or Cs_2CO_3) and solvents (THF, MeCN, or acetone) were examined with allyl bromide or allyl iodide as the alkylating partner.[14] With all conditions examined, the *O*-allylated product was the predominant product. Exclusive *N*-allylation of **20** was finally achieved under the palladium-catalyzed allylic substitution condition. By employing 2 mol % of $Pd(PPh_3)_4$ as the catalyst and 2 equiv of allyl methyl carbonate as the allylating reagent, the reaction went to completion within 1 h with excellent isolated yield (86%).[15] The ring closing metathesis of **21** using Grubbs II ruthenium complex (5 mol %) in refluxing CH_2Cl_2 gave the key lactam intermediate **22** in 85% yield (ca. 66% yield from **19**).[16,17]

Initial attempt to selectively hydrogenate the double bond without cleavage of trityl group by using $[Ir(cod)py(PCy_3)]PF_6$ complex (Crabtree catalyst, 5 mol %) with H_2 (1atm) was unsuccessful.[18] The homogeneous iridium complex seemed to serve as a Lewis acid, which caused ca. 30% detritylation based on LC−MS analysis. To avoid the potential coordination, 5 wt % Pt/C (5 mol % of Pt loading) was used as the catalyst under 1 atm of H_2 to afford **23** cleanly with no detectable amount of detritylation product.[19] The deprotection of *N*-Fmoc group under basic conditions, triethylamine in acetonitrile at rt, afforded 68% of **24** from **22**. The amide formation of **24** with (*R*)-3-hydroxybutyric acid using EDC and HOAt (1-hydroxy-7-azabenzotriazole) as the coupling reagents gave *O*-trityl cobactin T (**25**) in 70% isolated yield. Unfortunately, $MgBr_2$ was ineffective for the removal of the trityl group in **25**. Although $BF_3{\cdot}OEt_2$ did provide clean cleavage of trityl group with the same efficiency, relatively low isolated yield (45%) was obtained presumably due to the loss of product during extraction. To overcome the potential issue of aqueous solubility of the product, Amberlyst 15 ion-exchange resin in CH_2Cl_2/MeOH was employed. After stirring for 2 h, the product was filtered and then recrystallized from ethyl acetate and hexane to furnish (−)-Cobactin T (**18**) in 80% yield. The spectroscopic data of the synthetic sample were consistent in all respects (mp, $[\alpha]_D^{20}$, ^1H NMR, and ^{13}C NMR) to those reported by Miller's group.[12a,13a]

In conclusion, the Lewis acid mediated detritylation in the synthesis of *N*-hydroxyl amine derivatives, especially the hydroxamates, has been investigated. Although the coordination nature of *O*-trityl hydroxamate unit plays an important role in reaction efficiency, $MgBr_2$, $ZnBr_2$, and $BF_3{\cdot}OEt_2$ were found to be superior for the removal of trityl group. In addition, the Amberlyst 15 ion-exchange resin also provided a viable alternative in terms of the ease for purification. These mild and highly efficient detritylative conditions clearly demonstrate the potential utility in the synthesis of metalloproteinase inhibitors containing hydroxamate moiety. The synthetic application using trityl as the protecting group in the synthesis of (−)-Cobactin T was achieved in seven steps with 25% overall yield. In addition, the *N*-hydroxy lactam ring was rapidly assembled by ring closing metathesis which provides the opportunity for the synthesis of *dehydro*-mycobactin analogs that maybe useful in studies of drug resistance in strains of mycobacteria.

Experimental Section

Representative procedures for detritylation using $MgBr_2$ or $BF_3{\cdot}OEt_2$ are described below.

Preparation of *N*-Hydroxy 2-(9-Fluorenylmethoxycarbonyl)-amino-4-pentenoamide (9a). To a mixture of **1a** (1.0 mmol, 594 mg, 1.0 equiv) and $MgBr_2$ (5.0 mmol, 920 mg, 5.0 equiv) was added CH_2Cl_2 (10 mL) at room temperature. The yellow suspension was stirred at rt for 40 min and was then poured into EtOAc/H_2O (50 mL/50 mL). The organic layer was washed with brine (50 mL), dried (Na_2SO_4), and filtered. After removal of solvent, acetone (10 mL) and hexane (50 mL) were added sequentially to the crude product. The resulting solid was filtered and was washed with Et_2O/hexane (1/1, 50 mL). The product was dried to give 303 mg of **9a** (86%) as a white solid.

Preparation of *N*-Hydroxy (9-Fluorenyl)methyl carbamate (12). To a mixture of **4** (2.0 mmol, 994 mg, 1.0 equiv) in $CHCl_3$/MeOH (16 mL/4 mL) was added $BF_3{\cdot}OEt_2$ (4.0 mmol, 0.5 mL, 2.0 equiv) at room temperature. The mixture was stirred at rt for 45 min and was then poured into EtOAc/H_2O (100 mL/100 mL). The organic layer was washed with brine (100 mL), dried (Na_2SO_4), and filtered. After removal of solvent, CH_2Cl_2 (10 mL) and hexane (30 mL) were added sequentially to the crude product. The resulting solid was filtered and was washed with Et_2O/hexane (2/3, 20 mL). The product was dried to give 474 mg of **12** (93%) as a white solid.

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Supporting Information Available: Detailed experimental procedure and characterization data for all *O*-trityl protected precursors (**1**−**8**), detritylation products (**9**−**16**), intermediates (**20**−**25**), and (−)-Cobactin T (**18**) are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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