case rate constants and selectivities of active sites can only be calculated if the fraction modification x can be determined independently. For a strongly adsorbed modifier a rough lower limit of k^*_m can be estimated from the initial dependence of r_{obs} on the amount of modifier added.[15] For the case of toluene, where these conditions may be met, we obtain $k^*_m \geq 130\ s^{-1}$, corresponding to the turnover frequency of a modified site.

We would like to make the following statements concerning the reaction mechanism: (1) our analysis is in complete agreement with a simple two-cycle mechanism (linear relationship between ee_{obs} and $1/r_{obs}$); (2) adsorption of HCd on the Pt surface must be reasonably strong and/or only a small fraction of the surface platinum is modifiable (full modification effect is reached at extremely low HCd concentrations); (3) simple geometric considerations indicate that a modified ensemble should consist of one adsorbed cinchona molecule and 10–20 platinum atoms, in good agreement with the ratio $k^*_m/k'_m \geq 13$ found in toluene.[16]

The implications of the present mechanistic picture will be examined further.

(15) For large equilibrium constants we can substitute the approximation HCd = Pt_m into eq 1. Taking the derivative with respect to HCd gives an estimate of k^*_m.

(16) Ordered arrays of adsorbed cinchona alkaloids have been proposed as an alternative explanation for the observed enantioselection: (a) Thomas, J. *Angew. Chem. Adv. Mater.* **1989**, *101*, 1105. (b) Wells, P. B. *Faraday Discuss. Chem. Soc.* **1989**, *87*, 1.

Facile Reduction of Ethyl Thiol Esters to Aldehydes: Application to a Total Synthesis of (+)-Neothramycin A Methyl Ether

Tohru Fukuyama,* Shao-Cheng Lin, and Leping Li

Department of Chemistry, Rice University
Houston, Texas 77251

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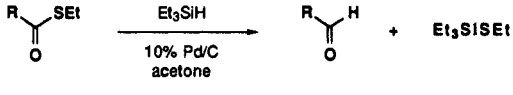
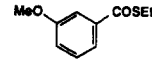
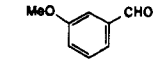
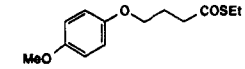
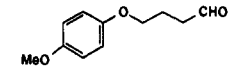
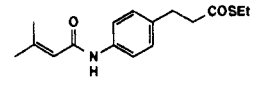
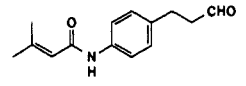
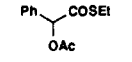
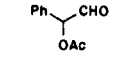
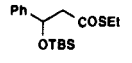
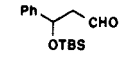
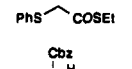
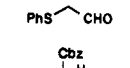
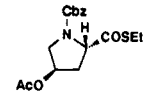
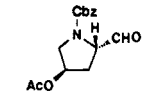
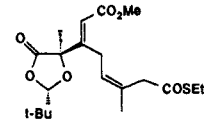
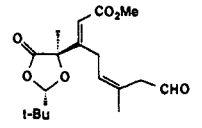
Transformation of carboxylic acids to aldehydes has been the subject of intensive investigation among synthetic organic chemists. With a few exceptions,[1] derivatives of acid such as acid chlorides, amides, and esters are usually converted to aldehydes by selective reduction. Although a number of synthetic methods have been reported to date, none seems to be generally applicable to multifunctional compounds. Hence the most frequently employed procedure at the present time is reduction of acid or its derivative followed by mild oxidation of the resultant alcohol. In this communication we report a highly efficient reduction of ethyl thiol esters to aldehydes with triethylsilane and a catalytic amount of palladium on carbon. Since acids can be readily converted to ethyl thiol esters under mild conditions,[2] this procedure provides a powerful alternative to the arsenal of synthetic chemists for transformation of acids to aldehydes. The versatility of our novel method is fully demonstrated in a total synthesis of (+)-neothramycin A methyl ether **11**.

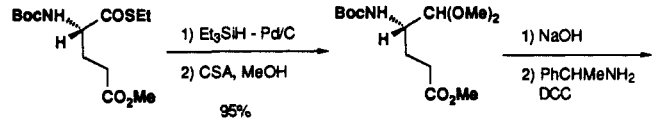


As shown in Table I, a variety of functional groups survive the essentially neutral reduction conditions.[3,4] Our method is suited for the conversion of optically active amino acids to amino aldehyde derivatives that are known to racemize even under mild conditions. For example, the optically pure thiol ester **1** was converted to the dimethyl acetal **2** in 95% yield in a 40-g-scale experiment. The optical purity of **2** was virtually 100% based on the ^1H NMR studies of the corresponding (*R*)-(+)-α-methylbenzylamide derivative **3**.[5]

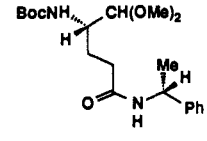
Table I. Reduction of Ethyl Thiol Esters with Triethylsilane and Palladium on Carbon

Entry	Substrate	Product	Yield (%)[a]
1			91[b]
2			94
3			97
4			84
5			88
6			75[b]
7			88[c]
8			92

[a] Isolated yields after chromatographic purification. [b] Isolated as tosylhydrazone. [c] Formation of the cis isomer was not observed.



1 **2**



3

To further demonstrate the usefulness of our procedure, neothramycins A and B (**4**)[6] were chosen as the target molecules for

(1) For representative examples, see: (a) Cha, J. S.; Kim, J. E.; Yoon, M. S.; Kim, Y. S. *Tetrahedron Lett.* **1987**, *28*, 6231. (b) Corriu, R. J. P.; Lanneau, G. F.; Perrot, M. *Tetrahedron Lett.* **1987**, *28*, 3941. (c) Brown, H. C.; Cha, J. S.; Nazer, B.; Yoon, N. M. *J. Am. Chem. Soc.* **1984**, *106*, 8001 and references cited therein.

(2) Ethyl thiol esters can be conveniently made in 60–85% yield from the corresponding acids via mixed anhydride in a one-pot procedure (EtOCOCl (1.2 equiv), Et_3N (2.4 equiv), CH_2Cl_2, 0 °C, 10 min; EtSH (2.3 equiv), then DMAP (0.1 equiv), 0 °C, 10 min). For conversion of protected amino acids and precious acids, Steglich's method was employed: Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.

(3) A general experimental procedure is as follows: To a stirred mixture of ethyl thiol ester (0.5–1 M solution) and 10% Pd on carbon (2–5 mol %) in acetone was added Et_3SiH (2–3 equiv) at room temperature under an argon atmosphere. Stirring was continued at room temperature until the reduction was completed (30–60 min). The catalyst was filtered off through Celite and washed with acetone. Evaporation and separation on a silica gel column gave the desired aldehyde in 80–97% yield. Methylene chloride can also be used as a solvent.

(4) The following functional groups are reduced under the reaction conditions and are incompatible: azide, nitro, and mono-substituted olefin.

(5) While the 300-MHz ^1H NMR spectrum of the amides derived from racemic glutamic acid 5-methyl ester exhibited two singlets at 3.33 and 3.41 ppm for the dimethyl acetal, the amide **3** derived from L-glutamic acid 5-methyl ester showed only a singlet at 3.33 ppm, and no trace of a peak at 3.41 ppm was observed.

(6) Isolation and structure determination: Takeuchi, T.; Miyamoto, M.; Ishizuka, M.; Naganawa, H. *J. Antibiot.* **1976**, *29*, 93. Synthesis: (a) Mori, M.; Uozumi, Y.; Ban, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 841. (b) Andriamialisoa, R. Z.; Langlois, N. *Tetrahedron Lett.* **1986**, *27*, 1149. (c) Miyamoto, M.; Kondo, S; Naganawa, H.; Maeda, K.; Ohno, M.; Umezawa, H. *J. Antibiot.* **1977**, *30*, 340.

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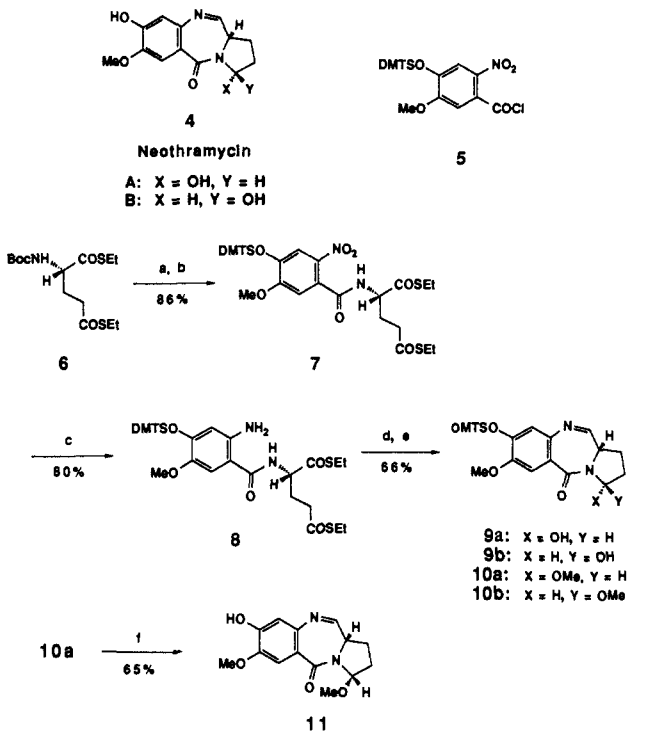
Scheme I[a]



[a] The reagents and reaction conditions were as follows: (a) BF_3·Et_2O (4 equiv), CH_2Cl_2, 23 °C. (b) **5** (1.2 equiv), saturated $NaHCO_3$, CH_2Cl_2, 23 °C. (c) Zn (excess), AcOH (8 equiv), Et_2O, 23 °C. (d) Et_3SiH (5 equiv), 10% Pd/C (15 mol %), dry CH_2Cl_2, Ar, 23 °C, 40 min. (e) CSA (0.1 equiv), MeOH, 23 °C. (f) n-Bu_4NF (1 equiv), AcOH (5 equiv), MeOH, 23 °C.

total synthesis (Scheme I). The L-glutamic dialdehyde backbone of the novel antitumor agents could potentially be constructed by simultaneous reduction of the corresponding L-glutamic dithiol ester. Thus the unstable amine derived from the readily available *N*-Boc-L-glutamic dithiol ester **6**[7] was acylated with the acid chloride **5**[8] to give the amide **7** in 86% yield from **6** ((1) BF_3·Et_2O (4 equiv), CH_2Cl_2; (2) **5**, saturated $NaHCO_3$, CH_2Cl_2). Reduction of the nitro group **7** with activated zinc furnished the amine **8** in 80% yield (Zn, AcOH, Et_2O). The critical double cyclization was performed by treatment with 10% Pd/C (15 mol %) and Et_3SiH (5 equiv) in CH_2Cl_2 at 23 °C for 40 min. The unstable neothramycin silyl ethers **9** thus formed were isolated as an epimeric mixture of the more stable methyl ethers **10** in 66% yield from **8** (CSA (camphorsulfonic acid), MeOH). Finally, deprotection of the dimethylthexylsilyl (DMTS) ether of the predominant α-epimer **10a** gave neothramycin A methyl ether **11** in 65% yield (n-Bu_4NF, AcOH, MeOH). The synthetic **11** proved to be identical with an authentic sample in both TLC behavior and spectroscopic properties.[9] The methyl ether **11** can be converted to neothramycin under mild acidic conditions.[6]

Acknowledgment. This work was supported by the Robert A. Welch Foundation (Grant C-0722) and the National Institutes of Health (Grant CA28119). We thank Dr. H. Naganawa of the Institute of Microbial Chemistry, Tokyo, for providing a generous sample of neothramycin A butyl ether. We also thank Mr. Yutaka Kanda for invaluable assistance.

(7) Prepared from *N*-Boc-L-glutamic acid in 73% yield (EtSH (6 molar equiv), DCC (2.5 molar equiv), DMAP (0.1 molar equiv), CH_3CN, 23 °C).

(8) Prepared from vanillin in six steps in 70% overall yield ((1) $PhCH_2Cl$, K_2CO_3, DMF, 100 °C; (2) fuming HNO_3, AcOH, 23 °C; (3) 12 N HCl–AcOH (1:3), reflux; (4) thexyldimethylsilyl chloride, imidazole, CH_3CN, 23 °C; (5) $KMnO_4$, t-BuOH, 5% NaH_2PO_4 buffer, 0 °C; (6) $(COCl)_2$, benzene, 60 °C).

(9) The average optical rotation of synthetic **11** was $[\alpha]^{25}_D$ +599° (c = 0.15, dioxane) (lit.[6] $[\alpha]^{26}_D$ +640° (c = 0.24, dioxane). It should be noted that the optical rotation of **11** is dependent on the amount of water in dioxane presumably because of hydration to the imine.

Supplementary Material Available: Experimental details for the preparation of **2** from L-glutamic acid 5-methyl ester and a listing of spectroscopic data of key intermediates for neothramycin A methyl ether synthesis (4 pages). Ordering information is given on any current masthead page.

Synthesis of a Highly Stable Iron Porphyrin Coordinated by Alkylthiolate Anion as a Model for Cytochrome P-450 and Its Catalytic Activity in O–O Bond Cleavage

Tsunehiko Higuchi, Shinobu Uzu, and Masaaki Hirobe*

Faculty of Pharmaceutical Sciences, University of Tokyo Bunkyo-ku, Tokyo 113, Japan

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Much interest has been focused on the mechanism of the catalytic cycle of cytochrome P-450.[1] One of the remarkable features of P-450 as a heme enzyme is that the heme iron of P-450 has a thiolate (RS^-) coordination.[1,2] Cytochrome P-450 is readily distinguished from other heme proteins spectrometrically because of the thiolate ligation. The thiolate ligand is therefore expected to strongly influence the chemistry of the heme iron. However, there have not yet been any experiments clearly directed toward revealing the relative effect of a thiolate ligand in P-450-type reactivity.[3,4]

Here we report on the synthesis and the catalytic activity of a novel iron porphyrin coordinated by thiolate anion which is highly stable during catalytic oxidations. The P-450 model **1** (Figure 1) was designed to introduce bulky groups on the RS^- coordination face of the porphyrin molecule so that the thiolate ligation could be highly stabilized and protected from oxidation. To prepare complex **1**, [*o*-[(acetylthio)methyl]phenoxy]acetic acid as a designed thiolate moiety was combined with *meso*-α,α,α,α-tetrakis(*o*-aminophenyl)porphyrin[5] and the remaining amino groups were all acylated with pivaloyl chloride to afford *meso*-α,α,α,α-[*o*-[[*o*-[(acetylthio)methyl]phenoxy]acetamido]phenyl]tris(*o*-pivalamidophenyl)porphyrin. After iron insertion and deprotection of the acetyl group, **1** was obtained as dark brown microcrystal.[6] Complex **1** was characterized by FAB-MS, IR, electronic absorption spectrum, EXAFS, and elemental analysis.[7] The EPR

(1) For recent reviews: (a) Ortiz de Montellano, P., Ed. *Cytochrome P-450*; Plenum: New York, 1986. (b) Dawson, J. H.; Sono, M. *Chem. Rev.* **1987**, *87*, 1255. (c) Mansuy, D. *Pure Appl. Chem.* **1987**, *59*, 759.

(2) Dawson, J. H. *Science* **1988**, *240*, 433.

(3) Sakurai et al. reported the oxidation of various compounds with a hemin/large excess amount of thiol/O_2 system although they did not pursue the *relative* effect of an axial ligand: Sakurai, H.; Hatayama, E.; Fujitani, K.; Kato, H. *Biochem. Biophys. Res. Commun.* **1982**, *108*, 1649 and references cited therein.

(4) Several P-450 chemical models having thiolate coordination have been reported though there are no experiments on catalytic oxidation with the models in these papers: (a) Traylor, T. G.; Mincey, T. C.; Berzinis, A. P. *J. Am. Chem. Soc.* **1981**, *103*, 7084. (b) Collman, J. P.; Groh, S. E. *Ibid.* **1982**, *104*, 1391. (c) Woggon, W.-D., Stäubli, B.; Fretz, H. *Helv. Chim. Acta* **1987**, *70*, 1174. (d) Schappacher, M.; Richard, L.; Fischer, J.; Weiss, R.; Bill, E.; Montiel-Montoya, R.; Winkler, H.; Trauwein, A. X. *Eur. J. Biochem.* **1987**, *168*, 419 and references cited therein.

(5) Collman, J. P.; Gagne, R. R.; Reed, C. A.; Harbert, T. R.; Lang, G.; Robinson, W. T. *J. Am. Chem. Soc.* **1975**, *97*, 1427.

(6) The temperature was kept below 30 °C throughout the procedure for the preparation of **1** in order to avoid the formation of atropisomers of the porphyrins. [*o*-[(Acetylthio)methyl]phenoxy]acetic acid (ATPA) was introduced from saligenin in three steps in high yield. Complex **1** was prepared from *meso*-α,α,α,α-tetrakis(*o*-aminophenyl)porphyrin via steps a–d: (a) ATPA, 2-chloro-1-methylpyridinium iodide, triethylamine (yield 53%); (b) pivaloyl chloride, pyridine (yield 76%); (c) $FeBr_2$, 2,4,6-collidine (yield 96%); (d) $NaOCH_3$ (yield 66%). Details of the procedure for the preparation of **1** will be described elsewhere.

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