A Novel Route to the Vinyl Sulfide Nine-Membered Macrocycle Moiety of Griseoviridin†

Enrico Marcantoni,* Massimo Massaccesi, and Marino Petrini

Dipartimento di Scienze Chimiche, via S. Agostino 1, I-62032 Camerino (MC), Italy

Giuseppe Bartoli,* Maria Cristina Bellucci, Marcella Bosco, and Letizia Sambri

Dipartimento di Chimica Organica "A. Mangini", v.le Risorgimento 4, I-40136 Bologna, Italy

Received January 27, 2000

The synthetic potentialities of cerium(III) chloride are demonstrated by the synthesis of a nine-membered ring heterocycle component of Griseoviridin (**3**) in optically active form. The key step involves the stereospecific formation of the α-carbalkoxy alkenyl sulfide moiety using a combination system of cerium(III) chloride heptahydrate and sodium iodide.

Introduction

The streptogramin antibiotics, for which the name streptogramin was derived from the soil microorganism *Streptomyces graminofaciens*, from which the antibiotic was first isolated in 1953,[1] have been known for the past five decades. During this time, they have proven to have many useful applications, in particular as a broad-spectrum antibiotic with in vitro inhibitory activity toward various pathogenic bacteria and fungi.[2] These antibiotics occur as two distinctly different classes of compounds. The antibiotics of group A are complex macrocyclic lactam−lactones, for which six structures have been reported to date,[3] and their structures have been confirmed by X-ray crystallography.[4] Virginiamycin M1 (**1**), Madumycin II (**2**), and Griseoviridin (**3**) are representative examples of type A (Figure 1).[5]

The antibiotics of group B, on the other hand, are hexadepsipeptides,[6] and, despite their quite different structures, the group A and B antibiotics in combination exhibit a strong synergism in their antibacterial action.[7]

As a synthetic challenge, we have been interested in one member of group A, Griseoviridin (**3**). The structure of Griseoviridin, the most structurally complex member of this class, was then determined and confirmed by single-crystal X-ray analysis.[8] Considerable progress has been reported in exploring novel synthetic routes to streptogramins of group A during these last years,[9] and the same synthetic effort has been recently applied to producing the key intermediates of Griseoviridin (**3**), for which, like Madumycin II (**2**),[10a] the total synthesis of Griseoviridin has recently been completed.[10b]

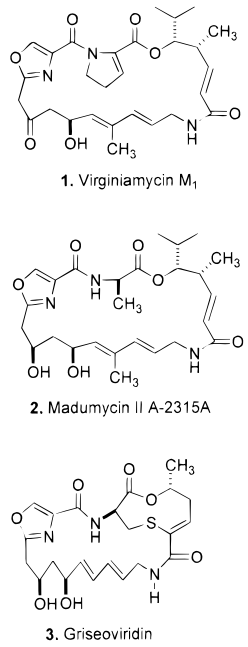


Figure 1.

A retrosynthetic scheme to the Griseoviridin (**3**) is outlined in Scheme 1. The simple disconnection at the amide bonds has revealed two fragments, **4** and **5**. Inspection of the target antibiotic reveals, in addition to a wide array of functionality, the presence of a rare

* To whom correspondence should be addressed. Tel: +39 0737 402255. Fax: +39 0737 637345. E-mail: enricom@camserv.unicam.it.

† This paper is dedicated to Professor Albert I. Meyers in recognition of his remarkable contribution to the art and science of organic chemistry.

(1) Charney, J.; Fisher, W. P.; Curran, C.; Machlowitz, R. A.; Tytely, A. A. *Antibiot. Chemother. (Washington, D. C.)* **1953**, 3, 1283.

(2) Ehrlich, J.; Coffey, G. L.; Fisher, M. W.; Galbraith, M. M.; Kundsen, M. P.; Sarber, R. W.; Schlingman, A. S.; Smith, R. M.; Weston, J. K. *Antibiot. Ann.* **1955**, 790.

(3) Bycroft, B. W. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2464−2470.

(4) Durant, F.; Evard, G.; Declerq, J. P.; Germain, G. *Cryst. Struct.* **1974**, 3, 503.

(5) (a) Paris, J. M.; Barriere, J. C.; Smith, C.; Bost, P. E. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lucas, G.; Ohno, M., Eds.; Springer-Verlag: Berlin, 1990; pp 183−248. (b) Di Giambattista, M.; Chinali, G.; Cocito, C. *J. Antimicrob. Chemother.* **1989**, 24, 485−488. (c) Cocito, C. *Microbiol. Rev.* **1979**, 43, 145−169.

(6) Sheehan, J. C.; Ledis, S. L. *J. Am. Chem. Soc.* **1973**, *95*, 875−879.

(7) Cocito, C. *J. Gen. Microbiol.* **1969**, 57, 179−184.

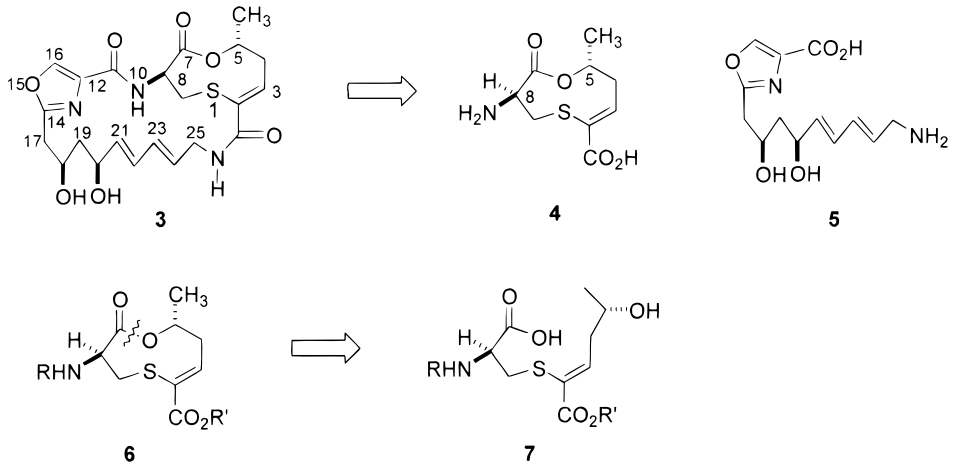
(8) Birubaum, G. L.; Hall, S. R. *J. Am. Chem. Soc.* **1976**, *98*, 1926−1931.

(9) (a) Bergdahl, M.; Hett, R.; Friebe, L. I.; Gangloff, R. A.; Iqbal, J.; Wu, Y.; Helquist, P. *Tetrahedron Lett.* **1993**, 34, 7371−7374. (b) Adje, N.; Breulles, P.; Uguen, D. *Tetrahedron Lett.* **1992**, 32, 2151−2154. (c) Kazmierczak, F.; Helquist, P. *J. Org. Chem.* **1989**, *54*, 3988−3992. (d) Meyers, A. I.; Lawson, J. P.; Walker, D. G.; Linderman, R. J. *J. Org. Chem.* **1986**, *51*, 5111−5123.

(10) (a) Tavares, F.; Lawson, J. P.; Meyers, A. I. *J. Am. Chem. Soc.* **1996**, *118*, 3303−3304. (b) Dvorak, C. A.; Schmitz, W. D.; Poon, D. J.; (Pryde, D. C.; Lawson, J. P.; Amos, R. A.; Meyers, A. I. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1664−1666.

10.1021/jo000116d CCC: $19.00
Published on Web 06/22/2000

Scheme 1



D-amino acid (C-8) and other chiral centers at C-5, C-18, and C-20. Two of these chiral centers, as well as the lactone and thiovinyl ether linkages, are present in the nine-membered macrocycle **4**, for which chemical degradations have unambiguously established the absolute configuration at C-5 and C-8. These developments have established that **4** possesses the 5R,8S configuration.[11] Further retrosynthetic analysis of the unusual sulfur-containing nine-membered lactone system **6** of Griseoviridin (**3**) has shown the presence of the conjugated vinyl sulfide moiety (**7**). Recently, the vinyl sulfides have attracted special attention as important intermediates in various synthetic transformations,[12,13] and their stereospecific synthesis has been attempted.[14]

In the course of our program, aimed to develop new synthetic uses of cerium trichloride, a very cheap, nontoxic, and water-tolerant reagent,[15] in reactions that need the presence of a Lewis acid activator, we have found several synthetically useful procedures using this trivalent lanthanide salt.[16] Moreover, during our studies on the applications of cerium compounds in organic synthesis, we have found that $CeCl_3 \cdot 7H_2O$, in conjunction with NaI, acts as an efficient reagent in the cleavage of the carbon−oxygen bond[17] under neutral conditions. Thus, we have considered the possibility of using cerium(III) chloride to promote the formation of the α-carboalkoxy alkenyl sulfide moiety in **7**, and we wish to report herein our recent results concerning a new strategy for the stereospecific synthesis of the N-protected nine-membered macrocycle **6** in pure enantiomeric form.

Results and Discussion

Griseoviridin **3**, one of the active compounds in the streptogramin family of antibiotics, has been the subject of synthetic studies for several years. The nine-membered ring heterocyclic component **6** has been previously prepared by three different approaches.[18−20] Because the formation of the conjugated vinyl sulfide moiety in **7** has been the most important, and at the same time, the most difficult, step in the three precedent sequences, our approach was to obtain this moiety through use of cerium(III) chloride.

Our synthetic approach began with the synthesis of S-methylcarboethoxy-D-cysteine derivative **12**. Therefore, we decided to start from D-cystine **8** (Scheme 2), which was transformed into the bis *tert*-butyl ester **9** by acid-catalyzed transesterification[21] of commercially available D-cystine with *tert*-butyl acetate. It is imperative to use a tightly stoppered flask in this reaction to prevent the loss of isobutylene and the corresponding reduction in yield. The formation of the bis benzamide **10** proceeds quite cleanly using benzoyl chloride and pyridine, affording a 92% recrystallized yield. The disulfide bond is then reductively cleaved using sodium borohydride in ethanol, producing the free thiol compound **11** in 70% yield after chromatography and crystallization. The final formation of carbon−sulfur bond in the intermediate **12** was obtained by deprotonation of the cysteinic sulfur and successive substitution of bromine atom in ethyl α-bromoacetate. It should also be mentioned that the S-methylethoxycarbonyl D-cysteine derivative is best prepared without racemization when sodium methoxide is used as the base.[22]

(11) (a) MacMillan, J.; Simpson, T. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1487−1491. (b) Kuo, C. H.; Taub, D.; Hoffsommer, R. D.; Wendler, N. L.; Urry, W. H.; Mullenbach, G. *J. Chem. Soc., Chem. Commun.* **1967**, 761−762. (c) Kuhn, R.; Kum, K. *Chem. Ber.* **1962**, *95*, 2009−2014.

(12) Takeda, T.; Kanamori, F.; Matsusito, H.; Fujiwara, T. *Tetrahedron Lett.* **1991**, 32, 6563−6566.

(13) Andres, D. F.; Laurent, E. G.; Marquet, B. S. *Tetrahedron* **1995**, 51, 2605−2608.

(14) Moshi, M.; Masuda, Y.; Arase, A. *J. Chem. Soc., Chem. Commun.* **1985**, 1068−1069.

(15) Imamoto, T. *Lanthanides in Organic Synthesis*; Academic Press: New York, 1994.

(16) (a) Liu, H. J.; Shia, K. S.; Shang, X.; Zhu, B. Y. *Tetrahedron* **1999**, 55, 3803−3830. (b) Alessandrini, S.; Bartoli, G.; Bellucci, M. C.; Dalpozzo, R.; Malavolta, M.; Marcantoni, E.; Sambri, L. *J. Org. Chem.* **1999**, *64*, 1986−1992. (c) Ballini, R.; Marcantoni, E.; Perella, S. *J. Org. Chem.* **1999**, *64*, 2954−2957. (d) Bartoli, G.; Bosco, M.; Dalpozzo, R.; De Nino, A.; Marcantoni, E.; Sambri, L. *J. Org. Chem.* **1998**, *63*, 3745−3747. (e) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Sambri, L. *Chem.−Eur. J.* **1997**, 3, 1941−1950. (f) Bartoli, G.; Marcantoni, E.; Petrini, M.; Sambri, L. *Chem.−Eur. J.* **1996**, 2, 973−979. (g) Bartoli, G.; Marcantoni, E.; Sambri, L.; Tamburini, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2046−2049.

(17) (a) Bartoli, G.; Bellucci, M. C.; Bosco, M.; Cappa, A.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **1999**, *64*, 5696−5699. (b) Bartoli, G.; Bosco, M.; Marcantoni, E.; Nobili, F.; Sambri, L. *J. Org. Chem.* **1997**, *62*, 4183−4184.

(18) Meyers, A. I.; Amos, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 870−872.

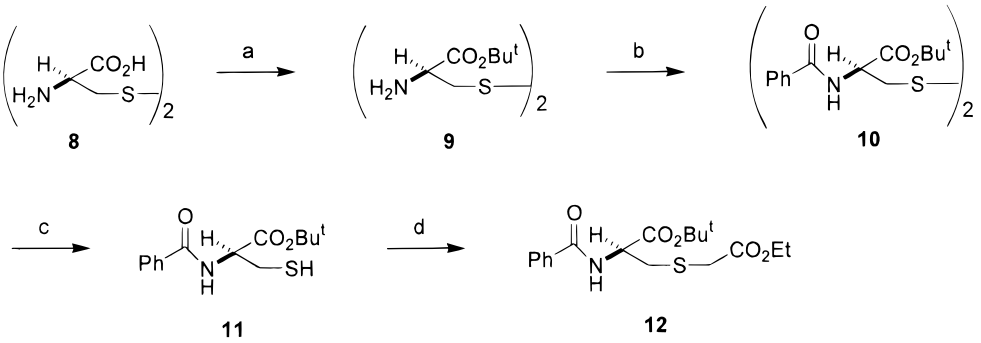
(19) Butera, J.; Rini, J.; Helquist, P. *J. Org. Chem.* **1985**, *50*, 3676−3678.

(20) Liu, L.; Yanke, R. S.; Miller, M. J. *J. Org. Chem.* **1986**, *51*, 5332−5337.

(21) Amaral, M. J. S. A.; Macedo, M. A.; Oliveira, M. I. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 205−206.

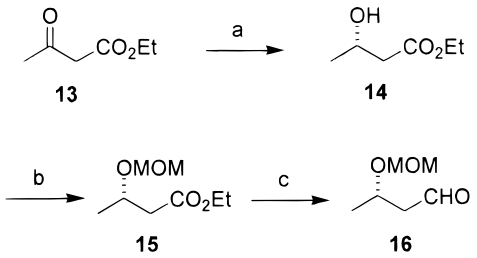
(22) Tamikaga, R.; Nozaki, Y.; Tamura, T.; Kaji, A. *Synthesis* **1983**, 134−135.

Scheme 2



[a] Key: (a) $CH_3CO_2Bu^t$, 60% $HClO_4$, r.t. 2 d, 83%; (b) PhCOCl, Pyridine, CH_2Cl_2, r.t. 15 h, 92%; (c) $NaBH_4$, EtOH, r.t. 1.5 h, 70%; (d) CH_3ONa, $BrCH_2CO_2Et$, CH_3OH, reflux 2 h, 86%.

Scheme 3



[a] Key: (a) Baker's yeast, 30 °C, 3 d, 70%; (b) $CH_2(OCH_3)_2$, $H_2C{=}CHCH_2SiMe_3$, I_2 (5% mol), r.t. 40 h, 90%; (c) DIBAL-H, CH_2Cl_2, −78 °C, 1 h 86%.

The C-3−C-5 fragment in the nine-membered ring of **4** was stereospecifically constructed as outlined in Scheme 3. In the interest of producing larger amounts and, more importantly, recognizing the need for a chiral molecule, the enantioselective reduction of ethyl acetoacetate (**13**) using a yeast fermentation broth[23,24] was found to proceed quite well. The chiral *β*-hydroxy ester **14** in 70% yield has proven to be in 95.4% enantiomeric excess (ee). The enantiomeric purity was checked by formation of the ester with (S)-(−)-1-methoxy-1-trifluoromethylphenylacetyl (MTPA) chloride, Mosher's chiral derivatizing agent.[25] It is important to note that the product from this reduction is (*S*) in configuration, opposite of the (*R*) required for the natural product. Thus, an inversion was necessary and was performed in the final ring-closure step.

The hydroxyl group was protected as methoxymethyl ether (MOM) **15**, frequently used as a protecting group for alcohols and phenols.[26,27] The MOM derivatives were usually prepared by alkylation with an excess of chloromethyl methyl ether.[28] Although this reagent is itself only a middling carcinogenic, it is usually contamined with small amounts of bis-chloromethyl ether, which is strongly carcinogenic.[29] For this reason the literature contains a variety of methods for the preparation of MOM ethers.[30] Very recently, Marcune *et al.*[31] reported that methoxymethyl-2-pyridylsulfide (MOM-ON) is an efficiently methoxymethylating reagent of hydroxyl groups of acid-sensitive molecules when used in conjunction with AgOTf, NaOAc, and THF. But the use of very expensive reagents prompted us to explore other methods, which have some advantages over using chloromethyl methyl ether. We have found that a suitable method is the transacetalization reaction of dimethoxymethane with *β*-hydroxy ester **14** utilizing iodotrimethylsilane generated in situ as a catalyst.[32] In fact, when a solution of hydroxy ester in dimethoxymethane was stirred in the presence of allyltrimethylsilane and catalytic iodine (5% mol), the methoxymethyl ether was obtained in good yield (90%). A lengthy reaction time (40 h) was required to ensure the complete consumption of the starting material. However, refluxing the reaction in dry benzene gives a shorter reaction time (15 h), but the yield is low (66%) and produces a lot of byproduct.

Diisobutylaluminum hydride (DIBAL-H) has proven to be a simple and versatile method[33] for the reduction of ester **15** to aldehyde **16** in 86% yield. The reduction was carried out at very low temperature (−78 °C), such that the ester moiety is still reactive to the hydride, but the aldehyde moiety is not.[33c] The difficulty with the solubility of the substrate, which occurs at the very low temperature in toluene, the solvent generally required in the use of DIBAL-H, was overcome using dichloromethane without a loss in the yield. With α-alkylthio ester **12** and aldehyde **16** in hand, we next examined the coupling of these two frameworks. The initial attempts to accomplish the Knoevenagel condensation (Scheme 4)

(23) (a) Seebach, D.; Giovannini, F.; Lamatsch, B. *Helv. Chim. Acta* **1985**, 68, 958−960. (b) Seebach, D.; Sutter, M. A.; Weber, R. H.; Züger, M. F. *Org. Synth.* **1984**, 63, 1−9.

(24) Dahl, A. C.; Fjeldberg, M.; Madsen, J. O. *Tetrahedron: Asymmetry* **1999**, 10, 551−559.

(25) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519. (b) Ohtani, I.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

(26) Greene, T. W. *Protective Groups in Organic Chemistry*; Wiley-Interscience: New York, 1981; p 10.

(27) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley & Sons: New York, 1967; Vol. 1, p 132.

(28) McComie, J. F. W. *Advances in Organic Chemistry*; Wiley-Interscience: New York, 1963; p 232.

(29) Occupational Safety and Health Administration, U. S. Department of Labor, Federal Register 39 (20); U. S. Government Printing Office: Washington, D. C., 1974.

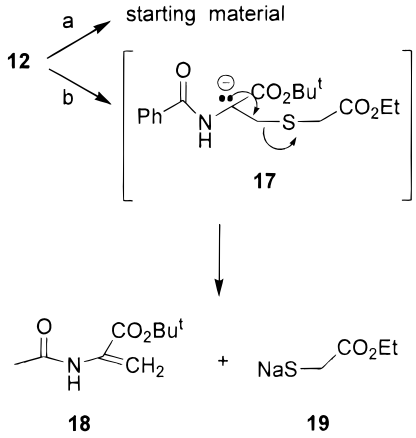
(30) (a) Kantam, M. L.; Sauthi, P. L. *Synlett* **1993**, 429−430. (b) Danheiser, R. L.; Romines, K. R.; Koyama, H.; Gee, S. K.; Johnson, C. R.; Medich, J. R. *Org. Synth.* **1992**, 71, 133−139. (c) Olah, G. A.; Husaine, A.; Gupta, B. G. B.; Narang, S. C. *Synthesis* **1981**, 471−472. (d) Yardley, J. P.; Fletcher, H. *Synthesis* **1976**, 244−245. (e) Fuji, K.; Nakano, S.; Fujita, E. *Synthesis* **1975**. 276−277.

(31) Marcume, B. F.; Karady, S.; Dolling, U.-H.; Novak, T. J. *J. Org. Chem.* **1999**, *64*, 2446−2449.

(32) Olah, G. A.; Husain, A.; Narang, S. C. *Synthesis* **1983**, 896−897.

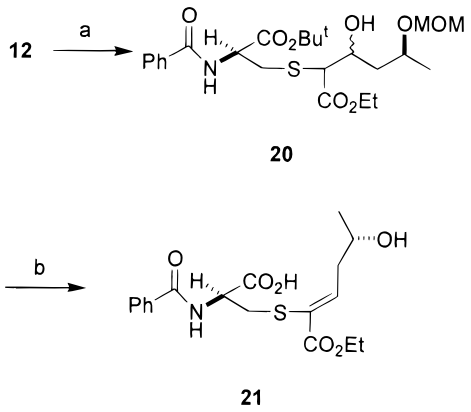
(33) (a) Keck, G. E.; Palani, A.; McHardy, S. F. *J. Org. Chem.* **1994**, *59*, 3113−3122. (b) Ito, Y.; Kobayashi, Y.; Kawabat, T.; Takase, M.; Terashima, S. *Tetrahedron* **1989**, 45, 5767−5790. (c) Johnstone, R. A. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, pp 259−281.

Scheme 4



[a] Key: (a) Piperidine, EtOH, **16**, r.t. 24 h; (b) NaH, THF, −78 °C, **16**, 2 h, 88%.

Scheme 5



[a] Key: (a) Bu^{t}MgCl, $CeCl_3$, THF, **16**, −78 °C, 6.5 h, 65%; (b) $CeCl_3 \cdot 7H_2O$, NaI, CH_3CN, reflux 24 h, 96%.

by the simple procedure of Tanikaga,[34] which uses reagents that are readily available and inexpensive, such as piperidine and ethanol, met with unsuccess. In every case, the starting ester **12** was recovered. An attempted condensation under treatment of ester **12** with NaH in THF at −78 °C resulted in removing the α-proton of cysteine moiety to afford carbanion intermediate **17**, which spontaneously eliminates the α-carboethoxymethylthiolate **19** to give α,*β*-unsaturated ester **18** as the major product. These observations suggested to us that the condensation is sensitive to the countercation and the degree of steric hindrance of the base employed for the anion generation.[35,36] From the literature, it is known that *tert*-butyl Grignard reagent may be used as a base to generate an anion in aldol condensation.[37] Moreover, it was found that dry cerium(III) chloride works as an efficient activator for the addition of carbanion to the carbonyl moiety.[38] Thus, the protected D-cysteine derivative **12** (Scheme 5) was converted to the magnesium derivative by reaction in THF with 1.35 equiv of *tert*-butylmagnesium chloride at −78 °C, and subsequent transfer by cannula to a mixture of chiral aldehyde **16** and dry $CeCl_3$ in THF at −78 °C, afforded a mixture of the desired diastereomeric alcohols **20** in 65% yield. Although both diastereomers were chromatographically separable, such separation was not necessary because dehydration of either mixture of the diastereomers proceeded efficiently. Attempted dehydration of **20**, by treatment with methanesulfonyl chloride and triethylamine, gave a complex mixture of elimination products. This problem was circumvented by repeating the dehydration using a combination system of $CeCl_3$ heptahydrate and sodium iodide in acetonitrile at reflux temperature.[39] Under these simple conditions, the (*Z*)-vinyl sulfide was exclusively obtained, and deprotection of the hydroxyl and carboxyl groups was also accomplished. The removal of the methoxymethyl protecting group by treatment with $CeCl_3 \cdot 7H_2O$/NaI system in acetonitrile has been reported,[40] whereas a new methodology to remove a *tert*-butyl ester has herein been reported, giving the penultimate product **21** in 96% yield as a white solid. The attempted column chromatography of the crude product led to low recoveries, due to difficulties in extracting the very polar hydroxy acid.

Finally, for the preparation of large-ring lactone from the corresponding open-chain hydroxy acid **21**, a rapid esterification reaction is necessary to overcome the unfavorable entropy factors leading to the formation of polymers. The mildness of the reaction conditions is also important if the method is to be applied to the synthesis of complex natural substances, such as Griseoviridin, with sensitive functionalities. Last decade, intensive studies in this field have commenced, and several good lactonization methods using different types of reagents have been developed,[41] some of them having been successfully applied to the synthesis of macrolides.[42] Consequently, the literature contains a variety of methods developed for the cyclization of medium and large ring lactones.[43] A limited number of those methods, however, appeared applicable to the problem in hand. Thus, the method employed has been an improved procedure of the Mitsunobu coupling reaction,[44,45] which uses the readily available reagents diphenyl-2-pyridylphosphine (Ph_2PyP) and di-*tert*-butylazodicarboxylate (DTBAD), respectively.[46] The reaction (Scheme 6) has been shown to proceed via

(34) Tanikaga, R.; Nishida, M.; Ono, N.; Kaji, A. *Chem. Lett.* **1980**, 781−782.

(35) Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1980**, *45*, 3549−3554.

(36) (a) Yamagiwa, S.; Hoshi, N.; Sato, H.; Kosugi, H.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1978**, 214−224. (b) House, H. O.; Crumrune, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310−3324.

(37) (a) Corey, E. J.; Weigel, L. O.; Cho, A. R. C. H.; Hua, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 6613−6615. (b) House, H. O.; Melillo, D. G.; Sauter, F. J. *J. Org. Chem.* **1973**, *38*, 741−748.

(38) (a) Bartoli, G.; Marcantoni, E.; Petrini, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1061−1062. (b) Imamoto, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 231−260. (c) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392−4398.

(39) Our results on the dehydration of *β*-hydroxy carbonyl compounds by the $CeCl_3 \cdot 7H_2O$/NaI system in acetonitrile at reflux temperature are submitted for publication.

(40) Bartoli, G.; Bosco, M.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Synlett* **1998**, 209−211.

(41) (a) Inanaga, J.; Hirata, K.; Saeri, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993. (b) Narasaka, K.; Masui, T.; Mukaiyama, T. *Chem. Lett.* **1977**, 763−765. (c) Nicolaou, K. C. *Tetrahedron* **1977**, 33, 683−710.

(42) (a) Narasaka, K.; Murayama, K.; Mukaiyama, T. *Chem. Lett.* **1978**, 885−887. (b) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585−607.

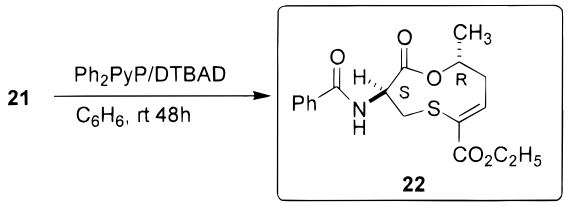
(43) Paterson, I.; Mausuri, M. M. *Tetrahedron* **1985**, 41, 3569−3624.

(44) Mitsunobu, O. *Synthesis* **1981**, 1−28.

(45) (a) Simon, C.; Sandor, H.; Sandor, M. *J. Heterocycl. Chem.* **1997**, 34, 349−356. (b) Hughes, D. L. *Org. React.* **1992**, 42, 335−398.

(46) Kiankarimi, M.; Lowe, R.; McCarthy, J. R.; Whitten, J. P. *Tetrahedron Lett.* **1999**, 40, 4497−4500.

Scheme 6



inversion of the hydroxyl center, thus allowing inversion of the (*S*) center obtained from the fermentation process into the required (*R*) configuration for Griseoviridin. It is crucial to the success of this lactonization that the hydroxy acid **21** is added very slowly, probably to avoid high stationary concentrations of hydroxy acid substrate. When the addition was complete, the mixture was additionally stirred several hours, to afford the desired lactone **22** in good yield (68%). Furthermore, by the combined use of the above two reagents, the purification of reaction product was easily achieved because the respective oxidation or reduction products of these reagents are either directly soluble in aqueous solution or are converted to gaseous byproducts. On the other hand, when the reaction was carried out in benzene at 25 °C, using the classical method of Mitsunobu reaction in high dilution conditions, the desired product was obtained in low yield (47%).[18]

In summary, we have provided an efficient route to the stereospecific preparation of the sulfur-containing nine-membered macrocycle N-protected moiety of Griseoviridin (**22**) in optically active form. We have also shown a method for the direct conversion in one step of the diastereomeric alcohols **20** to the corresponding hydroxy acid **21** required for the purpose at hand. We believe that the simplicity of this approach, the low cost of friendly reagents, the ease of use, and the high yield make manifest the synthetic potentialities of this procedure. Finally, further investigations obtaining the oxazole dienylamine moiety **5** necessary for the Griseoviridin synthesis are currently in progress in our laboratory.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra are reported at 200 and 50 MHz, respectively, and in $CDCl_3$ unless otherwise specified. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Flash column chromatography[47] was used to separate and purify the crude reaction mixtures. Anhydrous solvents were freshly distilled from either sodium benzophenone ketyl, or CaH_2.[48]

D-Cystine di-*tert*-Butyl Ester (9). The D-cystine (1 g, 4.16 mmol) was dissolved in 60% $HClO_4$, then 26 mL of *tert*-butyl acetate was added, and the mixture was sealed tightly with a glass stopper. The reaction was stirred for 2 d at room temperature, during which time a white precipitate formed. The mixture was cooled in a freezer for 24 h and then filtered. The white solid was washed with (2 × 20 mL) ether. The product was then neutralized (with extreme care) with saturated $NaHCO_3$ solution, extracted thoroughly with CH_2Cl_2, and dried over Na_2SO_4. After the solvent was removed, 1.22 g of a colorless oil was obtained , 83% crude yield, and used directly without purification in the next step.

***N*-Benzoyl D-Cystine di-*tert*-Butyl Ester (10).** The crude product **9** (0.68 g, 1.94 mmol) was diluted with 13 mL of dry CH_2Cl_2 and cooled to 0 °C, followed by the addition of 0.43 mL of pyridine and a dropwise addition of benzoyl chloride freshly distilled before use (0.67 g, 4.78 mmol) in 5 mL of dry CH_2Cl_2. After being maintained for 30 min at the same temperature, the mixture was warmed to room temperature and stirred for 15 h. The mixture was diluted with CH_2Cl_2, washed with brine containing sufficient 2N HCl to remove the amine, washed with saturated aqueous $NaHCO_3$, and dried over Na_2SO_4. The evaporation of the solvent gave a solid that was recrystallized from cyclohexane containing a minimum amount of $CHCl_3$. The solid can trap cyclohexane in the crystal structure, which can be removed by redissolving the product in $CHCl_3$ and stripping it to dryness three times. This yielded the isolated product **10**, 1.0 g (92% yield): mp 160−162 °C; $[\alpha]_D$ +25.0° (c = 1.84, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 18H), 3.36 (t, 4H, J = 5.33 Hz), 4.90−4.98 (m, 2H), 7.08 (d, 2H, J = 7.04 Hz), 7.35−7.49 (m, 6H), 7.78−7.82 (m, 4H). Anal. Calcd for $C_{28}H_{36}N_2O_6S_2$: C, 59.97; H, 6.47; N, 4.99; S, 11.43. Found: C, 59.95; H, 6.46; N, 4.95; S, 11.40.

***N*-Benzoyl D-Cysteine *tert*-Butyl Ester (11).** Disulfide **10** (1.46 g, 2.6 mmol) was suspended in 100 mL of absolute ethanol, and $NaBH_4$ (0.98 g, 26 mmol) was added portionwise. The reaction mixture was kept near 25 °C by means of an external water bath. The mixture was essentially homogeneous after 2 h and TLC indicated only traces of the disulfide. After the majority of the ethanol was stripped, the mixture was diluted with CH_2Cl_2, washed with saturated brine solution, extracted several times with CH_2Cl_2, and dried over Na_2SO_4. The product was purified by flash column chromatography (30% EtOAc/hexane), yielding 1.13 g of D-cysteine derivative (70% yield): mp 96−98 °C; $[\alpha]_D$ +40.02° (c = 1.5, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3370, 1730; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 1H, 8.85 Hz), 1.50 (s, 9H), 3.02−3.21 (m, 2H), 4.90−4.95 (m, 1H), 7.05 (d, 1H, J = 6.40 Hz), 7.40−7.53 (m, 3H), 7.80−7.84 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 27.00, 27.13, 28.06, 54.13, 54.21, 83.27, 127.09, 128.55, 131.92, 133.71, 169.24, 170.05. Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.76; H, 13.25, N, 4.97; S, 11.39. Found: C, 59.75; H, 13.22; N, 4.96; S, 11.39.

***tert*-Butyl(2*S*)-2-Benzoylamino-3-{[(1-ethoxycarbonyl)-methyl]thio}propanoate (12).** Sodium (0.075 g, 3.21 mmol) was dissolved in methanol (25 mL). To this solution was added, with stirring, a solution of N-benzoyl D-cysteine *tert*-butyl ester (0.9 g, 3.21 mmol) in methanol (10 mL) and a solution of ethyl bromoacetate (0.54 g, 3.21 mmol) in methanol (5 mL) at room temperature. The resulting mixture was refluxed for 1 h, then, after the methanol was stripped, neutralized with saturated aqueous NH_4Cl, and extracted thoroughly with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and evaporated, and the product **12** (1 g, 86% yield) was isolated as an oil by flash column chromatography (25% EtOAc/hexane): $[\alpha]_D$ −6.36° (c = 1.1, $CHCl_3$); IR (neat, cm^{-1}) 3356, 1735; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H, J = 7.15 Hz), 1.49 (s, 9H), 3.21 (t, 2H, J = 4.98 Hz), 3.26−3.37 (m, 2H), 4.13 (q, 2H, J = 7.20 Hz), 4.89−4.97 (m, 1H), 7.22 (, 1H, J = 7.25 Hz), 7.39−7.51 (m, 3H), 7.82−7.87 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.09, 27.07, 34.28, 52.91, 61.55, 83.04, 127.18, 128.54, 131.76, 133.77, 167.01, 169.67, 170.29; ESI-MS m/z 390 $[M + Na]^+$, 368 $[M + H]^+$, 334 $[M + Na - 56]^+$. Anal. Calcd for $C_{18}H_{25}NO_5S$: C, 58.83; H, 7.85; N, 3.81; S, 8.72. Found: C, 58.80; H, 6.81; N, 3.80; S, 8.72.

Ethyl (3*S*)-3-Hydroxybutanoate (14). A 2-L, two-necked, round-bottomed flask, equipped with mechanical stirrer and a reflux condenser, was charged with 560 mL of water at 30 °C, 105.2 g of sucrose, and 70.13 g of Baker's yeast, which were added with stirring in this order. After 1 h, ethyl acetoacetate 25 (7.0 g, 0.054 mmol) was added with thorough mixing. The broth was kept at 30 °C for 24 h, at which time the fermentation had essentially stopped. A warm (ca. 40 °C) solution of 70.13 g of sucrose in 350 mL of water was then added, and CO_2 evolution soon resumed. After 1 h, an additional keto ester (7.0 g, 0.054 mmol) was added, and the resulting mixture was kept at room temperature for 2 d. When the reaction is complete by gas chromatography−mass, the mixture was worked up by first adding 40 g of Celite and filtering through a Büchner funnel (17 cm diameter). After the filtrate was

(47) Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

(48) Leonard, J.; Lygo, B.; Procter, G. In *Advanced Practical Organic Chemistry*; Blackie Academic & Professional: London, 1990.

washed with 100 mL of water, saturated with sodium chloride, and extracts with five 150 mL portions of ethyl ether, the combined ether extracts were dried over Na_2SO_4, filtered, and concentrated with a rotary evaporator in a 35 °C bath temperature to a volume of 30−35 mL. This residue was fractionally distilled through a 10 cm Vigreux column, yielding 9.96 g of hydroxy ester **14**: bp 71−73 °C/12 mmHg; $[\alpha]_D$ +38.75° (c = 1, $CHCl_3$); IR (neat, cm^{-1}) 3440, 1730; ^1H NMR ($CDCl_3$) δ 1.17−1.25 (m, 6H), 2.32−2.42 (m, 2H), 2.80 (bs, 1H; OH), 4.09−4.17 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 14.14, 22.39, 42.77, 60.65, 64.23, 172.91; GC−MS m/z 131 $[M - 1]^+$, 117, 88, 87, 71, 60, 45, 31. Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.50; H, 9.15.

Ethyl (3*S*)-3-(Methoxymethoxy)butanoate (15). To a solution of the β-hydroxy ester **14** (3.5 g, 26.4 mmol) in dimethoxymethane (70 mL), allyltrimethylsilane (3.42 g, 30.8 mmol) and iodine (cat. 5% mol) were added, and the mixture was stirred at room temperature under a nitrogen atmosphere, while the progress of the reaction was monitored by GLC. After completion of reaction, the mixture was poured into a mixture of ether (300 mL), water (90 mL), and saturated sodium thiosulfate solution (9 mL). The organic layer was washed with water and saturated brine solution and dried over Na_2SO_4. Evaporation of solvent the crude product was purified by flash column chromatography on silica gel (30% EtOAc/hexane), yielding 4.22 g of a colorless oil[49] (90% yield): $[\alpha]_D$ +10.83° (c = 0.85, $CHCl_3$); IR (neat, cm^{-1}) 1735; ^1H NMR ($CDCl_3$) δ 1.15−1.30 (m, 6H), 2.48 (dd, 2H, J = 7.52 and 15.20 Hz), 3.31 (s, 3H), 4.05−4.20 (m, 3H), 4.62 (s, 2H); GC−MS m/z 175 $[M - 1]^+$, 161, 145, 131, 101, 73, 59, 43. Anal. Calcd for $C_8H_{16}O_4$: C, 54.53; H, 9.15. Found: C, 54.53; H, 9.12.

(3*S*)-3-(Methoxymethoxy)butanal (16). A 1.0 M solution of DIBAL-H in hexane (15 mL, 15 mmol) was added slowly to a solution of ester **15** (2.31 g, 13 mmol) in dry CH_2Cl_2 (100 mL) at −78 °C. After stirring at the same temperature for 1 h, methanol (15 mL) was added dropwise (destruction of the excess of DIBAL-H) and the mixture poured into 0.5N HCl (450 mL). After stirring for additional 1 h to room temperature, the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (120 mL, 6 times). The combined organic extracts dried over Na_2SO_4, evaporated and the residue purified by distillation to obtain 1.50 g of protected aldehyde,[50] yield 86%: bp = 65−68 °C/7.5 mmHg; $[\alpha]_D$ = +25.6° (c = 1.2, $CHCl_3$); IR (neat, cm^{-1}) 1731; ^1H NMR ($CDCL_3$) δ 1.25 (d, 3H, J = 6.0 Hz), 2.30−2.65 (m, 2H), 3.32 (s, 3H), 4.17 (sextet, 1H, J = 6.0 Hz), 4.55−4.75 (m, 2H), 9.75 (t, 1H, J = 2.0 Hz); GC−MS m/z 117, 114, 87, 75, 67, 41, 29. Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.51; H, 9.13.

***tert*-Butyl (2*S*)-2-(Benzoylamino)-3-{[(4*S*)-1-(ethoxycarbonyl)-2-hydroxy-4-(methoxy-methoxy)pentyl]thio}propanoate (20).** In a 100-mL three-necked round-bottom flask equipped with a magnetic stirrer and condenser, a dropping funnel of finely ground $CeCl_3 \cdot 7H_2O$ (0.36 g, 0.98 mmol) was dried by heating at 140 °C/0.1 mmHg for 2 h,[51,52] and then it was suspended in 20 mL of dry THF and left to stir overnight at room temperature. The white suspension was cooled to 0 °C, and a solution of chiral aldehyde **16** (0.090 g, 0.68 mmol) in 2 mL of THF was added and left stir for 1 h. To this mixture was transferred by cannula a THF (10 mL) solution of D-cysteine derivative **12** (0.24 g, 0.66 mmol), which has been precooled to −78 °C and in which a 1 M solution in ether of *tert*-butylmagnesium chloride was added dropwise. The resulting mixture was then left to stir untie TLC indicated that no substrate **12** remained (6.5 h). The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (35 mL). A standard workup with CH_2Cl_2 extraction and water and brine washing gave a viscous oil, which was chromatographed on silica gel column using ethyl acetate−hexane (40:60) as eluent to afford the two diastereomers (at the new chiral center) of **20** in a ratio of about 1:1 (the total yield was 0.21 g, 65%). Both diastereomers were oils. Diastereomer 1: $[\alpha]_D$ +15.6 (c = 1.05, $CHCl_3$); IR (neat, cm^{-1}) 3386, 1721; ^1H NMR ($CDCl_3$) δ 1.18−1.26 (m, 6H), 1.48 (s, 9H), 2.47−2.59 (m, 2H), 3.18−3.30 (m, 3H), 3.32 (s, 3H), 3.74−3.82 (m, 2H), 4.13 (q, 2H, J = 7.18 Hz), 4.63−4.67 (m, 2H), 4.91−4.95 (m, 1H), 7.30 (d, 1H, J = 7.32 Hz), 7.42−7.50 (m, 3H), 7.81−7.86 (m, 2H), 9.45 (bs, 1H); ESI-MS m/z 538 $[M + K]^+$, 522 $[M + Na]^+$. Anal. Calcd for $C_{24}H_{37}NO_8S$: C, 57.69; H, 7.46; N, 2.80; S, 6.42. Found: C, 57.68; H, 7.42; N, 2.80; S, 6.37. Diastereomer 2: $[\alpha]_D$ + 15.2° (c = 1.05, $CHCl_3$); IR (neat, cm^{-1}) 3386, 1720; ^1H NMR ($CDCl_3$) δ 1.18−1.23 (m, 6H), 1.46 (s, 9H), 2.40−2.49 (m, 2H), 3.18−3.30 (m, 3H), 3.32 (s 3,H), 3.79−3.86 (m, 2H), 4.13 (q, 2H, J = 7.18 Hz), 4.75−4.78 (m, 2H), 4.99−5.04 (m, 1H), 5.70 (bs, 1H), 7.21 (d, 1H, J = 7.32 Hz), 7.42−7.50 (m, 3H), 7.81−7.86 (m, 2H); ESI-MS m/z 538 $[M + K]^+$, 522 $[M + Na]^+$. Anal. Calcd for $C_{24}H_{37}NO_8S$: C, 57.69; H, 7.46; N, 2.80; S, 6.42. Found: C, 57.65, H, 7.40, N, 2.69; S, 6.41.

(2*S*)-2-(Benzoylamino)-3-{[(*Z*,4*S*)-1-(ethoxycarbonyl)-4-hydroxypent-1-enyl]thio}propanoic acid (21). A solution of a mixture of the diprotected diastereomeric alcohols **20** (98 mg, 0.196 mmol) in acetonitrile (3 mL) was treated with $CeCl_3 \cdot 7H_2O$ (0.11 g, 0.294 mmol) and NaI (29 mg, 0.196 mmol), and the resulting mixture was stirred at reflux temperature for 24 h (until no starting material remained, as monitored by TLC). The reaction mixture was diluted with EtOAc and treated with 0.5 N HCl (10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were evaporated, the residue was dissolved in 10% $NaHCO_3$ solution (25 mL), and the bicarbonate layer was washed with ether. Bicarbonate solution was then made acidic to pH = 3 and extracted with ethyl acetate. The organic extracts were washed with water and brine, dried over Na_2SO_4, and evaporated to give hydroxy acid **21** as a white solid (72 mg, 96% yield) with (*Z*)-configuration, not contaminated by any amount of the (*E*)-diastereomer. Diastereomeric purity was determined by NMR analysis: $[\alpha]_D$ +2.96° (c = 0.9, $CHCl_3$); mp 140−142 °C; IR (DMSO, cm^{-1}) 3470, 1770, 1730, 1694; ^1H NMR (DMSO) δ 0.95 (d, 3H, J = 6.15 Hz), 1.23 (t, 3H, J = 7.08 Hz), 2.26−2.49 (m, 2H), 3.26−3.62 (m, 2H), 4.12 (q, 2H, J = 7.12 Hz), 4.30−4.46 (m, 1H), 4.72−4.80 (m, 1H), 7.20−7.55 (m, 5H), 7.84 (d, 2H, J = 7.21 Hz), 8.68 (d, 1H, J = 8.06 Hz), 12.70 (bs, 1H); ESI-MS m/z 420 $[M + K]^+$, 404 $[M + Na]^+$. Anal. Calcd for $C_{18}H_{23}NO_6S$: C, 56.67; H, 6.07; N, 3.67; S, 8.41. Found: C, 56.63; H, 6.06; N, 3.65; S, 8.37.

Ethyl (5*R*,8*S*)-9-Benzoylamino-5-methyl-7-oxo-4,5,8,9-tetrahydro-7*H*-1,6-oxathionine-2-carboxylate (22). To a solution of diphenyl-2-pyridylphosphine (52.6 mg, 0.2 mmol) in dry benzene (90 mL) at room temperature under an atmosphere of nitrogen was added di-*tert*-butylazodicarboxylate (46 mg, 0.2 mmol) in one portion, and the resulting mixture was stirred for 30 min. A solution of hydroxy acid **21** (50 mg, 0.131 mmol predissolved in 4 mL of dry THF) in dry benzene (60 mL) was added dropwise over a period of 20 h to the vigorously stirred reaction mixture at room temperature. Upon completion of the addition, the mixture was stirred for 28 h at this temperature (the progress reaction was monitored by TLC). To the mixture was added 10% citric acid (25 mL), then the stirring was continued at room temperature for 1 h. After the majority of the benzene was stripped under reduced pressure, the product was extracted with CH_2Cl_2. The organic solution was washed with water, saturated solution $NaHCO_3$, and brine. The dried (Na_2SO_4) extracts were concentrated, and the crude product purified by flash column chromatography (40% EtOAc−hexane) giving 32.6 mg of a white solid (68% yield): $[\alpha]_D$ −126.5° (c = 1, $CHCl_3$); mp 128−130 °C; IR ($CHCl_3$, cm^{-1}) 3320, 1736, 1715; ^1H NMR ($CDCl_3$) δ 1.18 (t, 3H, J = 7.15 Hz), 1.33 (d, 3H, J = 6.67 Hz), 2.45−2.55 (m, 1H), 3.00−3.20 (m, 2H), 3.32−3.49 (m, 1H), 4.15 (q, 2H, J = 7.10 Hz), 4.96−5.01 (m, 1H), 5.20−5.30 (m, 1H), 7.01 (d, 1H, J = 6.33 Hz), 7.40−7.50 (m, 4H), 7.58−7.69 (m, 2H); ^{13}C NMR ($CDCl_3$)

(49) Cure, J.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1970**, 2962−2967.
(50) Yamamoto, Y.; Komatsu, T.; Murayama, K. *J. Organomet. Chem.* **1985**, 285, 31−42.
(51) Imamoto, T. *Org. Synth.* **1999**, 76, 228−238.
(52) The water molecule found in dry cerium(III) chloride seems to have no effect because the material was highly efficient without a large excess of organometallic compound. Cf. Evans, W. J.; Feldman, J. D.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 4581−4584.

δ 14.63, 18.39, 29.20, 35.00, 40.38, 52.20, 68.36, 126.27, 128.20, 131.54, 148.23, 166.15, 170.91; ESI-MS *m/z* 402 $[M + K]^+$, 386 $[M + Na]^+$. Anal. Calcd for $C_{18}H_{21}NO_5S$: C, 59.48; H, 5.82; N, 3.85; S, 8.82. Found: C, 59.45; H, 5.79; N, 3.84; S, 8.77.

Acknowledgment. Financial support from the University of Camerino and MURST (Research National Project "Stereoselection in Organic Synthesis. Methodologies and Applications) is gratefully acknowledged. The authors thank Dr. Giovanni Rafaiani for NMR experiments and Dr. Massimo Ricciutelli for mass spectrometry, as well as for every helpful discussions with Professor Albert I. Meyers (Colorado State University).

JO000116D