Total Synthesis of (+)-Hitachimycin

Amos B. Smith, III,* Thomas A. Rano, Noritaka Chida, and Gary A. Sulikowski

Department of Chemistry, the Laboratory for Research on the Structure of Matter, and the Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Received November 28, 1989

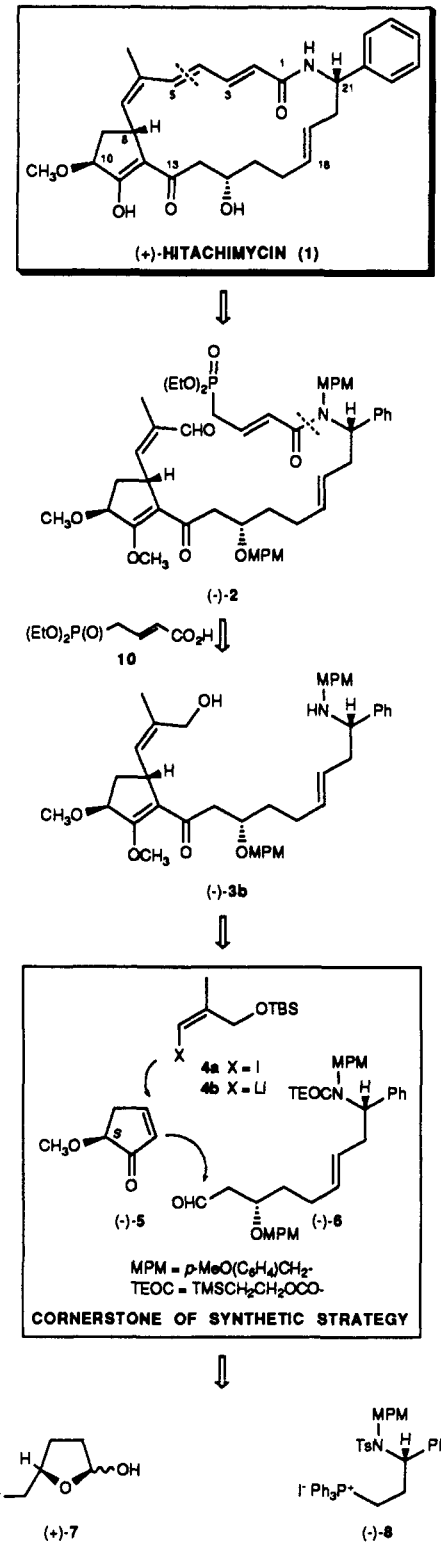
Summary: The first total synthesis of the macrocyclic antibiotic–antitumor agent (+)-hitachimycin (1) has been achieved via a convergent and efficient route (22 steps, 1.2% overall yield). The key transformation entailed a highly stereoselective, three-component coupling of (−)-5-methoxycyclopentenone (**5**) with a zincate derived from vinyl iodide **4a** and aldehyde (−)-**6**.

In collaboration with Ōmura, we recently defined the relative and absolute stereochemistry as well as the solid-state and solution conformations of the antitumor antibiotic macrolactam (+)-hitachimycin (stubomycin) (**1**).[1,2] Herein we report the first total synthesis of (+)-hitachimycin.

From the retrosynthetic perspective, **1** embodies an interesting array of functionality including an *E,E,Z*-triene unit and a cyclopentanone ring annulated to a 19-membered lactam (Scheme I). The 1,3-trans disposition of the C(10)-methoxy and C(8)-alkenyl substituents led us to consider a three-component coupling of (*S*)-5-methoxycyclopentenone (**5**)[3a] with an organometallic generated from vinyl iodide **4a** and aldehyde **6**, to furnish advanced intermediate **3b** after oxidation and deprotection. Critical in such a scenario would be the stereochemical outcome of the conjugate addition; model studies suggested that the requisite selectivity would in fact be realized.[3] Aldehyde **6**, with the correct absolute stereochemistry, was envisioned to arise via Schlosser–Wittig olefination[4] of bromo lactol **7** with the ylide prepared from phosphonium salt **8**; chain extension of the derived epoxide would then afford **6**. Homochiral **7** in turn would derive from (*S*)-(+)-glutamic acid, whereas **8** would be prepared from the methyl ester of (*S*)-(+)-β-phenyl-β-alanine (**9**).[5] For the northern perimeter, we envisioned a two-step sequence involving amide formation with phosphono acid **10**,[6] followed by a Horner–Emmons keto phosphonate macrocyclization.[7]

The synthesis of aldehyde (−)-**6** from (+)-**9** is outlined in Scheme II. The key transformation involved coupling

Scheme I



of (+)-**7** with the ylide derived from (−)-**8**. Unfortunately, all attempts to effect the Schlosser modification of the Wittig reaction with high trans stereoselectivity failed. We therefore executed a two-step procedure involving normal

(1) Smith, A. B., III; Wood, J. L.; Rizzo, C. J.; Furst, G. T.; Carroll, P. J.; Donohue, J.; Ōmura, S. *J. Org. Chem.*, preceding paper in this issue.

(2) For earlier investigations of 1, see: (a) Ōmura, S.; Nakagawa, A.; Tanaka, Y. *Trends Antibiot. Res.* **1982**, 135. (b) Umezawa, I.; Takeshima, H.; Komiyama, K.; Koh, Y.; Yamamoto, H.; Kawaguchi, M. *J. Antibiot.* **1981**, *34*, 259. (c) Komiyama, K.; Edanami, K.; Yamamoto, H.; Umezawa, I. *Ibid.* **1982**, *35*, 703. (d) Ōmura, S.; Nakagawa, A.; Shibata, K.; Sano, H. *Tetrahedron Lett.* **1982**, *23*, 4713. (e) Komiyama, K.; Edanami, K.; Tanoh, A.; Yamamoto, H.; Umezawa, I. *J. Antibiot.* **1983**, *36*, 301. (f) Komiyama, K.; Iwasaki, K.; Miura, M.; Yamamoto, H.; Nozawa, Y.; Umezawa, I. *Ibid.* **1985**, *38*, 1614. (g) Shibata, K.; Satsumabayashi, S.; Sano, H.; Komiyama, K.; Nakagawa, A.; Ōmura, S. *Ibid.* **1988**, *41*, 614. (h) Shibata, K.; Satsumabayashi, S.; Sano, H.; Komiyama, K.; Zhi-Bo, Y.; Nakagawa, A.; Ōmura, S. *Ibid.* **1989**, *42*, 718.

(3) (a) Smith, A. B., III; Dunlap, N. K.; Sulikowski, G. A. *Tetrahedron Lett.* **1988**, *29*, 439. The synthesis of (±)-**5** was based upon a published preparation of 5-ethoxy-2-cyclopentenone: DePuy, C. H.; Thurn, R. D.; Isaks, M. *J. Org. Chem.* **1962**, *27*, 744. (b) Smith, A. B., III; Trumper, P. K. *Tetrahedron Lett.* **1988**, *29*, 443.

(4) Schlosser, M.; Tuong, H. B.; Schaub, B. *Tetrahedron Lett.* **1985**, *26*, 311.

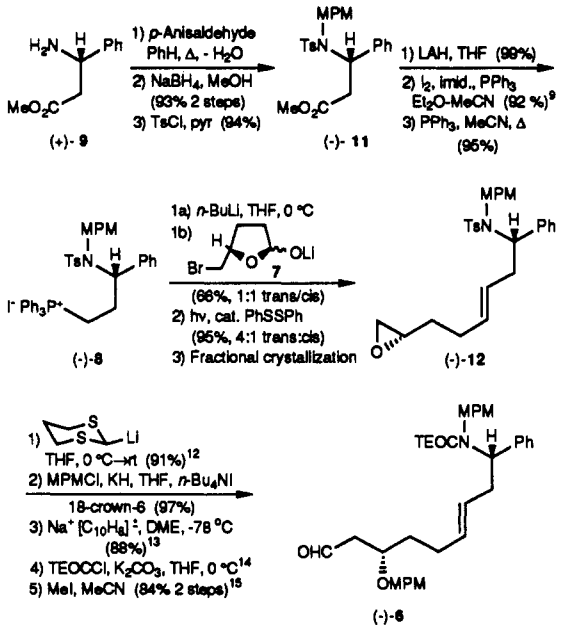
(5) Wasserman, H. H.; Berger, G. D. *Tetrahedron* **1983**, *39*, 2459.

(6) Floyd, D. M.; Fritz, A. W. *Tetrahedron Lett.* **1981**, *22*, 2847.

(7) Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069. Stork, G.; Nakamura, E. *J. Org. Chem.* **1979**, *44*, 4010. Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4013. Meyers, A. I.; Babiak, K. A.; Campbell, A. L.; Comins, D. L.; Fleming, M. P.; Henning, R.; Heuschmann, M.; Hudspeth, J. P.; Kane, J. M.; Reider, P. J.; Roland, D. M.; Shimizu, K.; Tomioka, K.; Walkup, R. D. *J. Am. Chem. Soc.* **1983**, *105*, 5015.

0022-3263/90/1955-1136$02.50/0

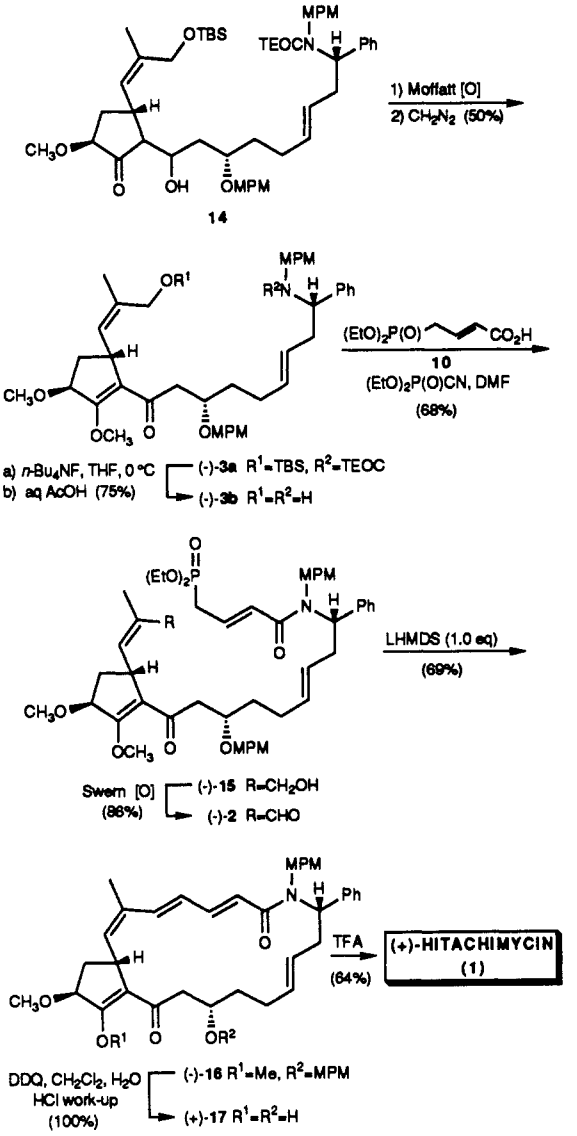
Scheme II



Wittig olefination followed by a photochemically-induced radical isomerization of the resultant isomer mixture. To this end, ylide formation (*n*-BuLi, THF, 0 °C) and addition of the deprotonated bromo lactol (+)-**7**[8,10] afforded epoxy olefin (−)-**12**[8] in 66% yield (1:1 trans/cis ratio). Radical isomerization[11] (3 mol % PhSSPh, *hν*) then efficiently generated a 4:1 trans/cis mixture from which the trans isomer could be fractionally crystallized. Several iterations of the irradiation/recrystallization sequence furnished multigram quantities of isomerically pure (−)-**12**.[8] A critical nitrogen protecting group interchange (Ts → TEOC)[13,14] and removal of the dithiane unit[15] afforded (−)-**6**.

With homochiral aldehyde (−)-**6** in hand, we began to explore the tricomponent assembly of **3** from **4a**, **5**, and **6**, the cornerstone of our synthetic strategy (Scheme I). Initial experiments focused on the Noyori three-component coupling,[16,17] using the cuprate reagent derived from vinyl iodide **4a**;[8a] the latter was prepared by silylation of the known *cis*-1-iodo-2-methylpropen-3-ol[18] (TBSCl, DMF, imidazole, 90%). The desired adduct (**14**, Scheme III), however, was obtained in less than 5% yield. Undaunted, we turned to the zincate coupling protocol developed more

Scheme III



recently by Noyori et al.[19] To our delight, reaction of enone (−)-**5** with the reagent generated from equimolar amounts of vinyllithium **4b** and bis(neopentyl)zinc[20] (ether, −78 °C, 1.5 h), followed by enolate trapping with (−)-**6** (1 equiv, −78 °C, 2.5 h), afforded **14**[8a] in 52% yield as a mixture of diastereomers.

The successful three-component coupling reaction set the stage for the final elaboration of (+)-hitachimycin as depicted in Scheme III. Central here was selective acylation of the secondary amine in (−)-**3b** with diethyl phosphonocrotonic acid (**10**),[6] effected via the Shioiri procedure (diethyl cyanophosphonate, DMF, 0 °C),[21] to give (−)-**15**[8a] in 68% yield. After Swern oxidation,[22] the crucial Horner–Emmons macrocyclization[7] was achieved by treatment of (−)-**2** with lithium hexamethyldisilazide (1 equiv, THF, −78 → 0 °C) to generate lactam (−)-**16**[8a] in 69% yield as a single isomer. Removal of the *O*-*p*-methoxybenzyl group at C(15) (DDQ, wet CH_2Cl_2)[23] followed

(8) (a) The structure assigned to each new compound was in accord with its infrared, 500-MHz ^1H NMR, and 125- or 62.5-MHz ^{13}C NMR spectra, as well as appropriate parent ion identification by high resolution mass spectrometry. (b) In addition, an analytical sample of this new compound gave satisfactory C and H combustion analysis.

(9) Marshall, J. A.; Cleary, D. G. *J. Org. Chem.* **1986**, *51*, 858.

(10) Bromo lactol **7** was prepared from γ-(hydroxymethyl)-γ-butyrolactone (Ravid, U.; Silverstein, R. M.; Smith, L. R. *Tetrahedron* **1978**, *34*, 1449) in two steps [(a) CBr_4, PPh_3; (b) DIBAL, CH_2Cl_2, −78 °C] in 99% yield.

(11) Thalmann, A.; Oertle, K.; Gerlach, H. *Org. Synth.* **1984**, *63*, 192 and references cited therein.

(12) (a) Seebach, D. *Synthesis* **1969**, 17. (b) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.

(13) Ji, S.; Gortler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1967**, *89*, 5311.

(14) Shute, R. E.; Rich, D. H. *Synthesis* **1987**, 346.

(15) Fetizon, M.; Jurion, M. *J. Chem. Soc., Chem. Commun.* **1972**, 382.

(16) (a) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847. (b) Suzuki, M.; Kawagishi, T.; Yanagisawa, A.; Suzuki, T.; Okamura, N.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1299. (c) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 4718.

(17) For a review of enolate trapping in conjunction with organocopper conjugate additions, see: Taylor, R. J. K. *Synthesis* **1985**, 364.

(18) Duboudin, J. G.; Jousseaume, B.; Bonakdar, A. *J. Organomet. Chem.* **1979**, *168*, 227.

(19) Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785.

(20) Bis(neopentyl)zinc was prepared via a method described previously for dimethylzinc: Greene, A. E.; Lansard, J.-P.; Luche, J.-L.; Petrier, C. *J. Org. Chem.* **1984**, *49*, 931. Also see: Kjonaas, R. A.; Hoffer, R. K. *J. Org. Chem.* **1988**, *53*, 4133. Tückmantel, W.; Oshima, K.; Nozaki, H. *Chem. Ber.* **1986**, *119*, 1581 and references cited therein.

(21) Yamada, S.; Kasai, Y.; Shioiri, T. *Tetrahedron Lett.* **1973**, 1595.

(22) Huang, S. L.; Omura, K.; Swern, D. *Synthesis* **1978**, 297.

by hydrolysis of the vinylogous ester (aqueous HCl workup) provided (+)-17[8a] quantitatively. Finally, exposure of (+)-17 to neat, anhydrous trifluoroacetic acid (room temperature, 2.5 h) removed the N-MPM moiety to afford crystalline (+)-hitachimycin (1) in 64% yield after chromatography. Synthetic 1 (mp 236–240 °C dec; mmp 236–240 °C) was identical in all respects including chiroptical properties with an authentic sample kindly provided by Professor Ōmura.

In summary, the first total synthesis of (+)-hitachimycin (1) has been achieved, confirming the assigned structure and absolute stereochemistry. The convergent and moderately effecient route (22 steps, 1.2% yield)[24] exploited a highly stereoselective conjugate addition to (*S*)-(−)-5-methoxycyclopentenone in the critical three-component coupling step.

Acknowledgment. Support for this investigation was provided by the National Institutes of Health (National Cancer Institute) through Grant CA-19033.

Supplementary Material Available: Spectroscopic and analytical data for **1**, **2**, **3a,b**, **4a**, **5–8**, **11–17**, and **i** (6 pages). Ordering information is given on any current masthead page.

(23) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.

(24) This sequence provided 81 mg of (+)-hitachimycin (1).

Biocatalytic Resolutions of α-Methylene-β-hydroxy Esters and Ketones

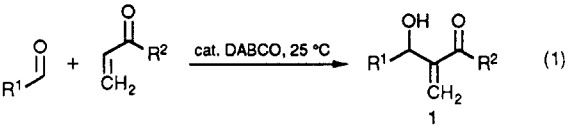
Kevin Burgess* and Lee D. Jennings

Rice University, Department of Chemistry, Box 1892, Houston, Texas 77251

Received November 21, 1989

Summary: α-Methylene-β-hydroxy esters and ketones are resolved via lipase mediated irreversible acylations;[1] experiments with a range of substrates have been used to identify factors that influence the enantioselection obtained and reaction times required.

α-Methylene-β-hydroxy esters and ketones are suitably functionalized for a multitude of chemical transformations.[2-5] They are easily prepared in racemic form via additions of α,β-unsaturated carbonyl compounds to aldehydes mediated by tertiary amine bases (reaction 1),[6] but their potential in *asymmetric* synthesis has not been exploited since there has been no truly convenient route to monochiral molecules of this type. Unfortunately, these allylic alcohols cannot be resolved via asymmetric Sharpless epoxidation[7-9] because of the deactivating influence of the electron-withdrawing alkene substituent. The most practical route to *optically active* α-methylene-β-hydroxy esters was, before this work, kinetic resolution of racemic samples via hydrogenation in the presence of monochiral transition-metal catalysts.[10-13] The scope of these resolutions with respect to substrate structure has not been reported, but certain limitations are evident; they are, for instance, clearly unsuitable for molecules containing other functionality vulnerable to reduction. Furthermore, manipulations of air-sensitive catalysts under elevated pressures of hydrogen are inconvenient, especially when the reaction must be stopped within a narrow conversion range to ensure good chemical and optical yields. Recent work in our laboratory led us to believe that biocatalytic acylations[14-16] of α-methylene-β-hydroxy carbonyl compounds in organic solvents[17,18] (reaction 2) could be enantioselective, cheap, and experimentally simple; this was confirmed in a preliminary study, the results of which are reported here.



(1)

1

Initial experiments with these resolutions (cf. reaction 2) demonstrated that crude *Pseudomonas AK* preparation (Amano) was slightly superior to *Pseudomonas K-10* (Amano) and these were more promising than any of the other enzymes tested (i.e. those from *Candida cylindracea*, *Geotrichum candidum*, *Rhizopus delemar*, and *Porcine pancreas* {Amano}). Illustrative results for the processes mediated by *Pseudomonas AK* are given in Table I.

Our findings indicate that enantiodiscrimination by the enzyme is high when R^2 is a "long chain" but not when this substituent is relatively short. For instance, the ratio of specificity constants (*E* values)[19] for acylation of the butyl ester in entry 1 is much greater than for the methyl ester in entry 4. The acylation is equally effective if R^2 is alkoxy or alkyl. Furthermore, aryl, alkyne, alkene, and sulfide entities in the R^2 substituent are tolerated by the enzyme without loss of enantioselection (entries 6, 3, 2, and 7, respectively); thus the enzyme can accommodate functional groups that would be destroyed under reductive conditions and others which could poison the transition-metal cata-

(1) Degueil-Castaing, M.; Jeso, B. D.; Drouillard, S.; Maillard, B. *Tetrahedron Lett.* **1987**, *28*, 953.
(2) Hoffman, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 795.
(3) Rabe, J.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1989**, *22*, 796.
(4) Hoffmann, H. M. R.; Rabe, J. *J. Org. Chem.* **1985**, *50*, 3849.
(5) Perlmutter, P.; Tabone, M. *Tetrahedron Lett.* **1988**, *29*, 949.
(6) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.
(7) Pfenninger, A. *Synthesis* **1986**, 89.
(8) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
(9) Carlier, P. R.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 2978.
(10) Brown, J. M.; Cutting, I. *J. Chem. Soc., Chem. Commun.* **1985**, 578.
(11) Brown, J. M.; Cutting, I.; Evans, P. L.; Maddox, P. J. *Tetrahedron Lett.* **1986**, *27*, 3307.
(12) Brown, J. M.; Evans, P. L.; James, A. P. *Org. Synth.* **1989**, 64.
(13) Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R.; Takaya, H. *J. Org. Chem.* **1988**, *53*, 708.
(14) Cambou, B.; Klibanov, A. M. *J. Am. Chem. Soc.* **1984**, *106*, 2687.
(15) Kirchner, G.; Scollar, M. P.; Klibanov, A. M. *J. Am. Chem. Soc.* **1985**, *107*, 7072.
(16) Cesti, P.; Zaks, A.; Klibanov, A. M. *Appl. Biochem. Biotech.* **1985**, *11*, 401.
(17) Zaks, A.; Klibanov, A. M. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 3192.
(18) Klibanov, A. M. *CHEMTECH* **1986**, 354.
(19) Chen, C.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.

0022-3263/90/1955-1138$02.50/0