In considering a general mechanism (Scheme I), it is possible that initially the highly electrophilic alkenyliodonium salt (**10**) reacts with the catalytic species Pd(0) [generated from the reduction of Pd(II) under the reaction conditions[5a]] followed immediately by the reductive elimination of iodobenzene and ligand coupling to yield an alkenyl palladium intermediate (**10** → **11** → **12**). Addition of this to the olefin (via the formation of a π-complex—(**12** → **13** → **14**), followed by reductive elimination would yield the coupled product (**14** → **15**) and Pd(0). Alternatively, it is possible that the initial step is a transmetalation between the alkenyliodonium salt and the palladium(II) catalyst which would also yield an alkenyl palladium intermediate similar to **12**. In fact, similar transmetalations[8] have been proposed for palladium-catalyzed coupling reactions of organomercury(II) compounds[9,5a] and organothallium(III) compounds.[10]

In summary, we consider the process reported herein to be a valuable addition to the Heck-type method because of its mild conditions, the wide range of structural types available, and its ease of operation.

Acknowledgment. We thank the National Science Foundation for the support (under Grant NSF CHE-8913012) of this work. Useful mechanistic discussions with Dr. Louis S. Hegedus are also gratefully acknowledged.

Supplementary Material Available: Experimental and spectroscopic data for compounds **5**, **7**, **9**, **4a,b**, **6a,b**, **8a,b**, and **10a,b** and NOE data (6 pages). Ordering information is given on any current masthead page.

(7) Rebrovic, L.; Koser, G. F. *J. Org. Chem.* **1984**, *49*, 4700. Stereochemistry of the isomers **7** and **9** were assigned from NOE experiments. The *Z* isomer (**9**) was crystallized in acetone (mp 167–169 °C, lit. 167–168.5 °C) while the *E* isomer was crystallized in ether (mp 145–147 °C, lit. 140–143 °C). Both were purified by recrystallization in hot acetone. The iodonium salt **5** (recrystallized in hot acetone) showed vinylic protons with a coupling constant of 12.3 Hz, hence, *E* stereochemistry was assigned to this.

(8) Palladium-catalyzed coupling reactions of both organomercurials and organothallium compounds[10a] proceed at room temperature as are the present coupling reactions of alkenyliodonium salts.

(9) (a) Larock, R. C. *Organomercury Compounds in Organic Synthesis*; Springer-Verlag: 1985. (b) Larock, R. C. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 27.

(10) (a) Kjonaas, R. A. *J. Org. Chem.* **1986**, *51*, 3708. (b) See, also: Uemura, S.; Zushi, K.; Okano, M.; Ichikawa, K. *J. Chem. Soc., Chem. Commun.* **1972**, 234.

Flexible Strategy to Polyfunctional Cyclopentanes. A Synthesis of Mannostatin A

Barry M. Trost* and David L. Van Vranken

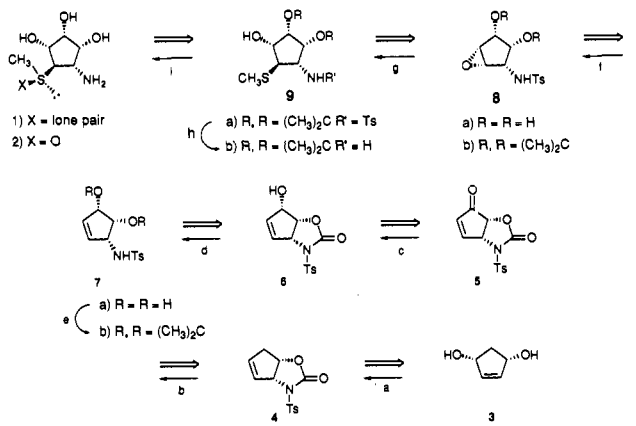
Department of Chemistry, Stanford University
Stanford, California 94305-5080

Received April 12, 1991

Particular interest has focused on glycosidase inhibitors as potential antiviral agents as well as antimetastatic, antitumor proliferative, or immunoregulatory agents.[1,2] Mannosidase inhibitors in particular have been promulgated as potential anti-HIV agents.[3] Great excitement and activity have revolved around the syntheses of several such inhibitors including nojirimycin,[4] swainsonine,[5,6] castanospermine,[6,7] and 1,5-dideoxy-1,5-imino-D-mannitol.[8] Mannostatin A (**1**) and B (**2**), isolated from *Streptoverticillium verticillus*, are highly specific nontoxic nanomolar inhibitors of α-D-mannosidase and represent the only known carbocyclic, naturally occurring mannosidase inhibitors.[9,10] The density of functionality and rich stereochemistry make such molecules extremely challenging targets for total synthesis. We record a highly flexible strategy for controlled introduction of heteroatoms around a cyclopentane nucleus, an increasingly important goal because of the growing number of cyclopentane analogues of carbohydrates as glycosidase inhibitors.

Scheme I outlines our retrosynthetic analysis, for which the key challenge is the chemo-, regio-, and diastereoselectivity of introduction of three different heteroatom functions on each carbon of a cyclopentane. While an asymmetric version of this synthesis is readily available via one of the scalemic analogues of **3** which derives from enzyme-catalyzed hydrolysis,[11] we chose to attempt to streamline the route by focusing on introducing the chirality

Scheme I. Retrosynthesis and Synthesis of Mannostatin A[a]



[a] (a) TsNCO (2 equiv), THF, add 1.8 mol % $[(iC_3H_7O)_3P]_4Pd$, reflux, 97%; (b) SeO_2, Na_2HPO_4, quartz sand, diglyme, 170 °C, followed by Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, room temperature, 65%; (c) $NaBH_4$, $CeCl_3$, CH_3OH, C_2H_5OAc, −5 °C, 83%; (d) K_2CO_3, CH_3OH-H_2O, room temperature, 95%; (e) $(CH_3)_2C(OCH_3)_2$, $(CH_3)_2CO$, CSA, room temperature, 93%; (f) CF_3CO_3H, Na_2HPO_4, CH_2Cl_2, 90%; (g) CH_3SLi, THF, −78 °C to room temperature, 78%; (h) Na, NH_3, 97%; (i) 60% aqueous CF_3CO_2H, 60 °C, 86%.

(1) Fellows, L. E. *New Sci.* **1989**, *123*, 45. Fellows, L. E. *Chem. Br.* **1987**, *23*, 842. Humphries, M. J.; Matsumoto, K.; White, S. L.; Molyneux, R. J.; Olden, K. *Cancer Res.* **1988**, *48*, 1410. Liu, P. S. *J. Org. Chem.* **1987**, *52*, 4717. Denis, J. W. *Cancer Res.* **1986**, *46*, 5131. Trugan, G.; Rousset, M.; Zweibaum, A. *FEBS Lett.* **1986**, *195*, 28. Sazak, V. V.; Ordovas, J. M.; Elbein, A. D.; Berninger, R. W. *Biochem. J.* **1985**, *232*, 759.

(2) Also, see: Tong, M. K.; Papandreou, G.; Ganem, B. *J. Am. Chem. Soc.* **1990**, *112*, 6137. Buchanan, J. G.; Lumbard, K. W.; Sturgeon, R. J.; Thompson, D. K.; Wightman, R. H. *J. Chem. Soc., Perkin Trans.* **1990**, 699. Farr, R. A.; Peet, N. P.; Kang, M. S. *Tetrahedron Lett.* **1990**, *31*, 7109.

(3) Winkler, D. A.; Holan, G. *J. Med. Chem.* **1989**, *32*, 2084 and references therein. Also, see: Walker, B. D.; Kowalski, M.; Goh, W. C.; Kozarsky, K.; Krieger, M.; Rosen, C.; Rohrschneider, L.; Haseltine, W. A.; Sodroski, J. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 8120. Montefiori, D. C.; Robinson, W. E., Jr.; Mitchell, W. M. *Antiviral Res.* **1989**, *11*, 137. Sunkara, P. S.; Bowlin, T. L.; Liu, P. S.; Sjoerdsma, A. *Biochem. Biophys. Res. Commun.* **1987**, *148*, 206.

(4) Inouye, S.; Tsuruoka, T.; Niida, T. *J. Antibiot., Ser. A* **1966**, *19*, 288. Anzeveno, P. B.; Creemer, L. J. *Tetrahedron Lett.* **1990**, *31*, 2085. Chida, N.; Furuno, Y.; Ogawa, S. *J. Chem. Commun.* **1989**, 1230 and references therein.

(5) Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* **1979**, *32*, 2257. Pearson, W. H.; Lin, K. *Tetrahedron Lett.* **1990**, *31*, 7571. Bennett, R. B., III; Choi, J. R.; Montgomery, W. D.; Cha, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 2580. Dener, J. M.; Hart, D. J.; Ramesh, S. *J. Org. Chem.* **1988**, *53*, 6022 and earlier references therein.

(6) Miller, S. A.; Chamberlin, A. R. *J. Am. Chem. Soc.* **1990**, *112*, 8100.

(7) Hohenschutz, L. D.; Bell, E. A.; Jervess, P. J.; Leworthy, D. P.; Pryce, R. J.; Arnold, E.; Clardy, J. *Phytochemistry* **1981**, *20*, 811. Bhide, R.; Mortezaei, R.; Scilimati, A.; Sih, C. J. *Tetrahedron Lett.* **1990**, *31*, 4827. Anzeveno, P. B.; Angell, P. T.; Creemer, L. J.; Whalon, M. R. *Tetrahedron Lett.* **1990**, *31*, 4321 and references therein.

(8) Ezure, Y.; Ojima, N.; Konno, K.; Mujazaki, K.; Yamada, N.; Sugiyama, M.; Itoh, M.; Nakamura, T. *J. Antibiot.* **1988**, *41*, 1142. Cf.: Fleet, G. W. J.; Gough, M. J.; Smith, P. W. *Tetrahedron* **1987**, *43*, 3083. Eis, M. J.; Rule, C. J.; Wurzburg, B. A.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 5397.

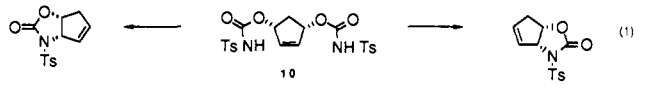
(9) Aoyagi, T.; Yamamoto, T.; Kojiri, K.; Morishima, H.; Nagai, M.; Hamada, M.; Takeuchi, Umezawa, H. *J. Antibiot.* **1989**, *42*, 883.

(10) Morishima, H.; Kojiri, K.; Yamamoto, T.; Aoyagi, T.; Nakamura, H.; Iitaka, Y. *J. Antibiot.* **1989**, *42*, 1008.

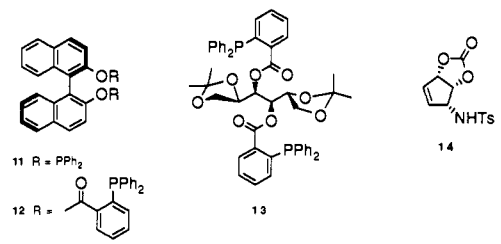
(11) Deardorff, D. R.; Matthews, A. J.; McMeekin, D. S.; Craney, C. L. *Tetrahedron Lett.* **1986**, *27*, 1255. Laumen, K.; Reimerdes, E. H.; Schneider, M. *Tetrahedron Lett.* **1985**, *26*, 407. Wang, Y.; Chen, C.; Girdankas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 3695. Muira, S.; Kurozumi, S.; Toru, T.; Tonaka, T.; Kobayashi, M.; Matsubara, S.; Ishimoto, S. *Tetrahedron Lett.* **1976**, 1899. For example, for a Pd(0)-catalyzed application of such asymmetric derived analogues, see: Deardorff, D. R.; Linde, R. G., II; Martin, A. M.; Shulman, M. S. *J. Org. Chem.* **1989**, 54, 2759.

0002-7863/91/1513-6317$02.50/0

as a consequence of oxazolidin-2-one synthesis[12] via cyclization of the bis-urethane derived from diol **3**[13] (eq 1). In contrast to



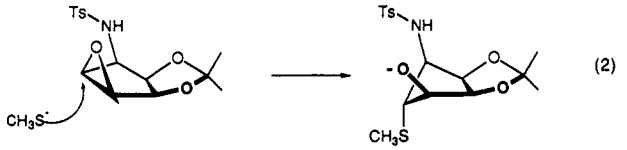
(1)



our synthetic efforts directed toward allosamizoline,[14] the Pd-catalyzed cyclization with BINAPO (**11**) as ligand gave only 28% ee. Interestingly, the conformationally less rigid diester ligand **12** (S-BDPBB) enhanced the selectivity to 41%, $[\alpha]^{25}_D$ -56.9 (*c* 3.92, CH_2Cl_2). *Gratifyingly, the c_2 symmetric diester* ***13*** *((+)-BIBDPBM), an example of a new class of very simply derived asymmetric ligands, jumps the ee to 65%,* $[\alpha]^{25}_D$ *+90.7 (c 2.49, CH_2Cl_2) (5 mol % $(dba)_3Pd_2{\cdot}CHCl_3$, 15 mol % **13**, THF, -8 to 20 °C, quantitative yield), of the 1R,2S enantiomer as determined by the O-methylmandelate ester NMR shifts*! The feasibility of an asymmetric synthesis having been demonstrated, biological considerations induced us to focus initially on racemic mannostatin.

Allylic oxidation without rearrangement of the double bond required strenuous conditions using selenium dioxide in which quartz sand was added to maintain dispersion of the reactants (mechanical stirring recommended). Since the resultant alcohol was frequently admixed with considerable quantities of the ketone, the mixture was normally directly oxidized. Of a horde of oxidants, only reaction with MnO_2[15] and the Dess-Martin periodinane[16] proceeded cleanly, the latter being preferred since the reaction went to completion. The third asymmetric center was then set by reduction.[17] The correctness of the stereochemistry was readily apparent by the facility with which the alcohol **6** isomerized to the carbonate **14**. Various attempts to hydroxysulfenylate **6** or **7a** failed due to the lack of reactivity of the double bond. On the other hand, the diol **7a** smoothly succumbed to epoxidation with trifluoroperacetic acid (CH_2Cl_2, Na_2CO_3, 86%) to give a single epoxide tentatively assigned as all-cis on the basis of the high level of directionality observed in the reactions of this reagent with allylic alcohols and ethers.[18]

With the stereochemistry all set, the last issue was the regioselective introduction of the methylthio group. Various attempts to promote regioselective opening by coordination with oxyphilic Lewis acids led to mixtures at best. For example, coordination of **8a** with titanium tetraisopropoxide[19] followed by lithium thiomercaptide led to a 1:1 regioisomeric mixture from which the desired thioether **9** (R = H, R′ = Ts) could be isolated in 21% yield. *On the other hand, the acetonide **8b** generates a 4.6:1 ratio of the two regioisomers in favor of our desired product **9a***! A possible explanation for this remarkable regioselectivity may derive from a Fürst-Plattner type stereoelectronic control[20] in which attack at the desired position involves a conformationally more favorable transition state as depicted in eq 2.[21] Completion of



(2)

the synthesis involves detosylation and hydrolysis to give mannostatin A. Passing an aqueous solution of the trifluoroacetate salt through the base form of an IRA 400 ion-exchange resin gives racemic mannostatin A as the free base. Comparison of the spectral data to that of an authentic sample indicated their identity. This route provides mannostatin A in 27% overall yield in 10 steps.

This strategy should prove to be a powerful approach to these types of cyclopentane analogues of carbohydrates. The synthetic intermediates readily available provide great flexibility to vary the regio- and diastereoplacement of the functionality. Furthermore, the ready incorporation of a phosphine ligand into asymmetric alcohols by esterification with the readily available 2-(diphenylphosphino)benzoic acid[22] should prove useful for asymmetric catalysis.

Acknowledgment. We thank the National Institutes of Health for their generous support of our programs. This material is based upon work supported by a National Science Foundation graduate fellowship. We thank Professor Takaaki Aoyagi for comparison data and a sample of mannostatin B. Mass spectra were provided by the Mass Spectrometry Facility, University of California—San Francisco, supported by the NIH Division of Research Resources.

Supplementary Material Available: Characterization data for **1** and **4-9** (2 pages). Ordering information is given on any current masthead page.

(12) Trost, B. M.; Sudhakar, A. *J. Am. Chem. Soc.* **1987**, *109*, 3792; **1988**, *110*, 7933. Trost, B. M.; Hurnaus, R. *Tetrahedrofn Lett.* **1989**, *30*, 3893.
(13) Kaneko, C.; Sugimoto, A.; Tanaka, S. *Synthesis* **1974**, 876.
(14) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 1261.
(15) Corey, E. J.; Crouse, D. *J. Org. Chem.* **1968**, *33*, 298. Pratt, E. F.; Van de Castle, J. F. *J. Org. Chem.* **1961**, *26*, 2973.
(16) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(17) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(18) McKittrick, B. A.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 4895.
(19) Sharpless, K. B.; Caron, M. *J. Org. Chem.* **1985**, *50*, 1560.
(20) Smith, J. G. *Synthesis* **1984**, 629. Winterfeldt, E. *Stereoselektive Synthese. Principien und Methoden*; F. Vieweg & Sohn: Braunschweig, 1988; pp 32-7. *Seances* Fürst, A.; Plattner, P. A. *Helv. Chim. Acta* **1949**, *32*, 275.
(21) Vidal, J.-P.; Granger, R.; Girard, J. P.; Rossi, J.-C.; Sablayrolles, C. *R. Seances Acad. Sci., Ser. C* **1972**, *274*, 905. Tabushi, I.; Fujita, K.; Oda, R. *J. Org. Chem.* **1970**, *35*, 2383.
(22) Hoots, J. E.; Rauchfuss, T. B.; Wrobleski, D. A. *Inorg. Synth.* **1982**, *21*, 178.

α-Cyano-α-fluorophenylacetic Acid (CFPA): A New Reagent for Determining Enantiomeric Excess That Gives Very Large ^{19}F NMR Δδ Values

Yoshio Takeuchi,*,† Noriaki Itoh,† Hiroshi Note,† Toru Koizumi,† and Kentaro Yamaguchi‡

Faculty of Pharmaceutical Sciences
Toyama Medical & Pharmaceutical University
Sugitani, Toyama 930-01, Japan
School of Pharmaceutical Sciences, Showa University
Hatanodai, Shinagawa-ku, Tokyo 142, Japan
Received March 25, 1991

Rapid progress has been made in the development of methods for asymmetric synthesis and in their application in the construction of complex natural products. Consequently, the determination of enantiomeric excess (ee) is an indispensable process for evaluating the efficiency of those methods. Herein we describe a unique multifunctional chiral tertiary fluoride,[1] α-cyano-α-fluorophenylacetic acid (CFPA, **1**), which has remarkable efficacy for determining ee, surpassing MTPA (**2**) in reactivity and ^{19}F NMR Δδ values.

CFPA (**1**) MTPA (**2**)

†Toyama Medical & Pharmaceutical University.
‡Showa University.
(1) (a) Takeuchi, Y.; Asahina, M.; Nagata, K.; Koizumi, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2203. (b) Takeuchi, Y.; Asahina, M.; Murayama, A.; Hori, K.; Koizumi, T. *J. Org. Chem.* **1986**, *51*, 955.

0002-7863/91/1513-6318$02.50/0