# Total Synthesis of (+)-Trehazolin: Optically Active Spirocycloheptadienes as Useful Precursors for the Synthesis of Aminocyclopentitols

Brian E. Ledford and Erick M. Carreira*

*Contribution No. 9121, Arnold and Mabel Beckman Laboratory for Chemical Synthesis, California Institute of Technology, Pasadena, California 91125*

*Received August 11, 1995*

Aminocyclopentitol-derived natural products such as allosamidin, mannostatin A, and trehazolin have been shown to be potent inhibitors of glycosidases (Figure 1). These glycoside processing enzymes play critical roles in intra- and intercellular processes including cell adhesion and recognition, membrane transport, and signal transduction. Consequently, the use of such compounds and their analogs as glycosidase inhibitors has important implications in immunology, virology, and oncology.[1] In addition to their remarkable biology, these natural products are challenging synthetic targets and offer an opportunity to develop reaction methodology for the construction of substituted cyclopentanes. Three general strategies have been employed for the synthesis of such five-membered rings: (1) heterocycloaddition reactions of substituted cyclopentadienes,[2] (2) desymmetrization reactions of substituted cyclopentenyl-1,4-*meso*-diols,[3,4] and (3) fragmentation and refunctionalization reactions of carbohydrates.[5] We have been interested in the development of a versatile chiral synthon that provides access to heterosubstituted cyclopentanes.[6] In this communication, we report an enantioselective synthesis of trehazolin which utilizes optically active 1-(hydroxymethyl)spiro[2.4]cyclohepta-4,6-diene (**6**) as starting material, obtained in multigram quantities from (*R*)-(−)-epichlorohydrin and cyclopentadiene.

In our retrosynthesis, two subunits, **4** and **5**, are generated upon disconnection of the glycosidic C−N bond (Scheme 1). Central to the analysis is the recognition that **4** may be prepared from spirocycloheptadiene **6**. Its use as starting material imparts versatility into the route since numerous synthetic transformations of the diene moiety and the cyclopropyl carbinol can be envisioned. Moreover, because (+)- and (−)-glycidol derivatives are commercially available, either enantiomer of the aminocyclopentitol may be prepared. The second subunit generated upon retrosynthetic disconnection is a glycosyl isothiocyanate, **5**. It was anticipated that a protected form of **5** (for example, R = Bn) could be prepared efficiently from 1,6-anhydroglucose (**7**), itself available from pyrolysis of corn starch.[7]

Preparation of optically active **6** was without precedence.[8,9] The synthesis of nonracemic **6** from an optically active glycidol derivative and metal cyclopentadienide (MCp) would require regiocontrol in the initial displacement reaction (Scheme 2), with the enantioselectivity of **6** depending on the relative rates of epoxide opening (path a) versus $S_N2$ displacement of C−X (path b). Initial results were not encouraging; for example, treatment of NaCp (2 equiv) with (+)-*O*-tosylglycidol yielded **6** as a racemate. After investigating various glycidol derivatives and MCp, reaction conditions were developed which gave desired optically active (*R*)-**6**. Treatment of lithium cyclopentadienide (CpH + BuLi) with (*R*)-epichlorohydrin (**8**)[10] afforded **6** in 60% yield (Scheme 3). Conversion of **6** to the corresponding Mosher ester and analysis by $^1$H NMR spectroscopy revealed that the spirocyclization reaction had occurred in 91% ee.[11]

Conversion of **6** to the corresponding trichloroacetimidate was effected upon treatment of **6** with NaH and $Cl_3CCN$.[12] From **9**, we were prepared to install the requisite 1,4-amino alcohol functionality in a stepwise manner. However, upon treatment of **9** with I(*sym*-collidine)$_2$ClO$_4$ (aqueous $CH_3CN$, 0 °C), **10** was obtained directly in 61% yield. Although we have not, to date, isolated any intermediates from the reaction mixture, the formation of **10** is consistent with an allylic iodide that suffers

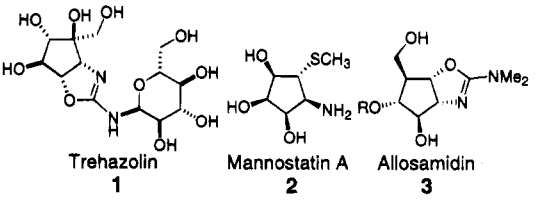
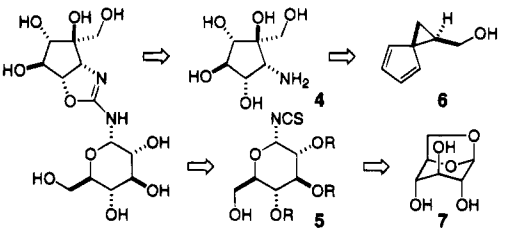
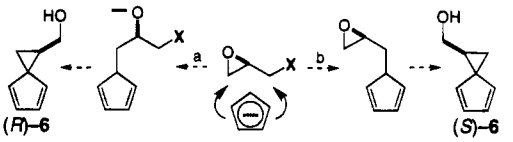



**Figure 1.** Aminocyclopentitol-derived natural products.

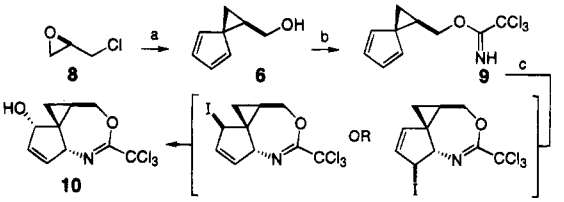
**Scheme 1**



**Scheme 2**



**Scheme 3**[a]



[a] Conditions: (a) NaH, CpLi, THF, 60%; (b) NaH, $Cl_3CCN$, THF, 95%; (c) I(*sym*-collidine)$_2$ClO$_4$, $NaHCO_3$, aqueous $CH_3CN$, 61%.

(1) Elbein, A. *Annu. Rev. Biochem.* **1987**, *56*, 497.

(2) (a) King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1991**, *113*, 5089; (b) **1994**, *116*, 562. (c) Goering, B. K.; Ganem, B. *Tetrahedron Lett.* **1994**, *35*, 6997. (d) Hansel, J.-G.; O'Hogan, S.; Lensky, S.; Ritter, A. R.; Miller, M. J. *Tetrahedron Lett.* **1995**, *36*, 2913.

(3) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 5863.

(4) (a) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1991**, *113*, 6317; (b) **1993**, *115*, 444.

(5) (a) Knapp, S.; Murali Dhar, T. G. *J. Org. Chem.* **1991**, *56*, 4096. (b) Nakata, M.; Akazawa, S.; Kitamura, S.; Tatsuta, K. *Tetrahedron Lett.* **1991**, *32*, 5363. (c) Simpkins, N. S.; Stokes, S.; Whittle, A. J. *Tetrahedron Lett.* **1992**, *33*, 793. (d) Uchida, C.; Yamagishi, T.; Ogawa, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 589 and references therein. (e) Kobayashi, Y.; Miyazaki, H.; Shiozaki, M. *J. Org. Chem.* **1994**, *59*, 813, and references therein. (f) Li, C.; Fuchs, P. L. *Tetrahedron Lett.* **1994**, *35*, 5121. (g) Kiguchi, T.; Tajiri, K.; Ninomiya, I.; Naito, T.; Hiramatsu, H. *Tetrahedron Lett.* **1995**, *36*, 253. (h) Takahashi, S.; Inoue, H.; Kuzuhara, H. *J. Carbohydr. Chem.* **1995**, *14*, 273.

(6) Two independent syntheses of trehazolin using carbohydrate starting materials have been reported: from resolution of an intermediate derived from *myo*-inositol, see ref 5d; from glucose, see ref 5e.

(7) Zemplen, G.; Gerecs, A. *Ber Dtsch. Chem. Ges.* **1931**, *64*, 1545.

(8) Racemic spiro[2.4]cyclohepta-4,6-diene has been employed as starting material in the synthesis of 12-methylprostaglandin $A_2$, see: Corey, E. J.; Shiner, C. S.; Volante, R. P.; Cyr, C. R. *Tetrahedron Lett.* **1975**, 1161.

(9) When the racemic synthesis of **6** was first reported, its structure was assigned incorrectly, see: Schaltegger, H. *Helv. Chim. Acta* **1962**, *45*, 1368. The correct structure was established later, see: Bangert, K.; Boekelheide, V. *Tetrahedron Lett.* **1963**, 1119.

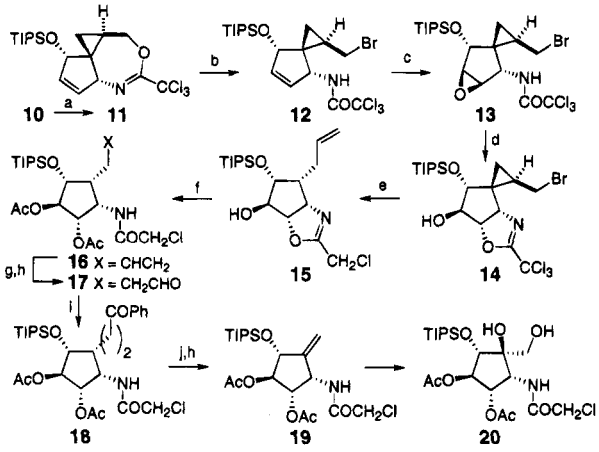
(10) We have found that (*R*)-1-chloro-2-hydroxy-3-(tosyloxy)propane (prepared from tosylglycidol and HCl) in the presence of 1 equiv of NaH can be utilized in the reaction mixture to generate epichlorohydrin *in situ*. For a synthesis of this reagent, see: Baldwin, J. J.; Raab, A. W.; Mensler, K.; Arison, B. H.; McClure, D. E. *J. Org. Chem.* **1978**, *43*, 4876. Tosylglycidol has been synthesized using the Sharpless asymmetric epoxidation reaction, see: Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 1295.

(11) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(12) Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597.

0002-7863/95/1517-11811$09.00/0 

**Scheme 4**[a]



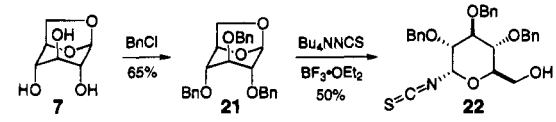
[a] Conditions: (a) $^{i}Pr_3SiOTf$, 2,6-lutidine, $CH_2Cl_2$, 95%; (b) $Li_2NiBr_4$, THF, 80%; (c) $Me_2CO_2$, acetone, 65%; (d) $BF_3{\cdot}OEt_2$, 87%; (e) $Bu_3SnH$, $Et_3B$, $NaBH_4$, EtOH, 75%; (f) PPTS, aqueous $CH_3CN$ and then $Ac_2O$, DMAP, 77% (two steps); (g) $Chx_2BH$, $H_2O_2$, 83%; (h) $(COCl)_2$, DMSO, $Et_3N$, 83%; (i) PhMgBr, LiBr, THF, 60%; (j) $h\nu$ and then $OsO_4$, NMO, 79%.

*in situ* hydrolysis under the reaction conditions, installing the desired 1,4-aminocarbinol in a single step.[13]

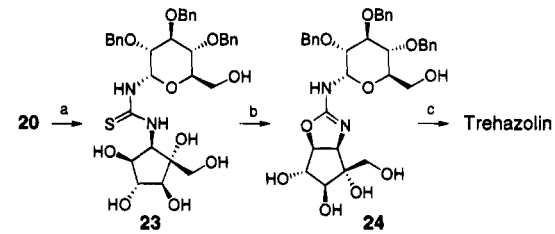
Silylation of the secondary carbinol in **10** yielded **11** in 95% yield (Scheme 4). Upon treatment of **11** with $Li_2NiBr_4$ in THF (2 equiv of LiBr + $NiBr_2$), the imidate underwent nucleophilic opening to yield cyclopropylcarbinyl bromide **12** in 80% yield.[14] The use of $Li_2NiBr_4$ in this ring-opening reaction represents a new application of this reagent, which has been used exclusively to effect opening of epoxides.[15] The alkene in **12** was converted to epoxide **13** upon treatment with a solution of dimethyldioxirane in acetone.[16] The epoxide subsequently underwent opening by the vicinal trichloroamide upon treatment with $BF_3{\cdot}OEt_2$ in toluene, giving **14** (87%).

Having fully functionalized the cyclopentadiene fragment, the spiro-fused cyclopropyl carbinyl moiety was excised. Fragmentation was effected upon reaction of **14** under free-radical conditions ($Bu_3SnH$, $Et_3B$, and $NaBH_4$), which also resulted in partial reduction of the trichloromethyl moiety. Oxazoline **15** was directly converted into **16** upon treatment with aqueous PPTS, followed by acetylation with $Ac_2O$ (77%, two steps). Hydroboration of the terminal alkene ($Chx_2BH$, $Et_2O$), followed by oxidation of the resulting primary alcohol, provided aldehyde **17**.[17,18] Conversion of **17** to the corresponding phenyl ketone was conducted upon treatment of **17** with PhMgBr and oxidation of the resulting secondary carbinol (89%). Aryl ketone **18** underwent Norrish Type II cleavage upon irradiation through a Pyrex filter in degassed benzene, giving alkene **19** in quantitative yield, which, without purification, was reacted with catalytic $OsO_4$ (NMO, aqueous acetone) to yield **20** as a single diastereomer, as determined by $^1H$ NMR spectroscopy (75% yield, two steps).

**Scheme 5**



**Scheme 6**[a]



[a] Conditions: (a) 4 N HCl and then **22**, DMAP, MeOH, 77%; (b) HgO, $Et_2O/Me_2CO$; (c) PdOH/C, $H_2$ (1 atm), MeOH, 40%.

Preparation of the glycosyl isothiocyanate subunit **22** for coupling to **20** was investigated next. In the reported syntheses, the coupling partner tetra-*O*-benzyl-α-D-glucose isothiocyanate was prepared in five steps from D-glucose.[19] A more efficient synthesis of tri-*O*-benzyl-α-D-glucose isothiocyanate was developed utilizing 1,6-anhydro-β-D-glucose, which is commercially available or, alternatively, conveniently prepared by pyrolyzing corn starch (Scheme 5). Bicyclic ketals such as **7** and **21** are known to be remarkably resistant to ring-opening reactions.[20] Nevertheless, treatment of **21** with $(Bu_4N)SCN$ and $BF_3{\cdot}OEt_2$ in toluene (23 °C, 48 h) provided **22** in 50% yield (83% based on recovered starting material).

With both fragments **20** and **22** in hand, the final coupling, cyclization, and deprotection procedures for the completion of the synthesis of trehazolin paralleled that previously reported by Shiozaki, who employed the 6-*O*-benzyl derivative of **22**.[5e] Treatment of **20** with 4 N HCl (60 °C, 8 h) yielded aminocyclitol **4** (Scheme 6). The unpurified aminocyclitol **4** was dissolved in pyridine/DMF and treated with isothiocyanate **22** to provide **23** (77%).[21] Closure of the thiourea to the desired glycosyl oxazoline **24** was effected upon treatment of **23** with yellow HgO. Finally, deprotection of the trehazolin *O*-tribenzyl ether (**24**) afforded synthetic trehazolin, identical in all respects to the natural product ($\alpha_D$, NMR, TLC).

In conclusion, an enantioselective synthesis of trehazolin from optically active 1-(hydroxymethyl)spiro[2.4]hepta-4,6-diene (**6**) has been presented; the fully functionalized aminocyclopentitol core is prepared in 14 steps by a sequence of reactions involving intermediates that may be readily accessed and differentially functionalized. The synthetic route is highlighted by (1) preparation of optically active **6**, (2) one-step amidohydroxylation of the cyclopentadiene subunit, (3) imidate opening with $Li_2NiBr_4$, and (4) the use of 1,6-anhydro-β-D-glucose in the preparation of the glycosylating reagent. Optically active **6** and its synthetic transformations should find use in the construction of other highly functionalized, stereochemically complex cyclopentyl rings.

**Acknowledgment.** We gratefully acknowledge the NIH and Upjohn, Pfizer, and Merck for support. We thank Dr. Nakajima (Sankyo Co., Ltd.) and Professor S. Ogawa (Keio University) for generously providing samples of (+)-trehazolin as well as spectral data for comparison.

**Supporting Information Available:** Experimental details and characterization data for **6**, **9**–**18**, **20**, **22**, and **23** (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA952749T

(13) Bromination of acyclic 1,3-dienes to give 1,2 (kinetic) versus 1,4 (thermodynamic) addition products has been investigated as a function of reaction solvent and temperature, see: (a) Farmer, E. H.; Lawrence, C. D.; Thorpe, J. F. *J. Chem. Soc.* **1928**, 729. (b) Hatch, L. F.; Gardner, P. D.; Gilbert, R. E. *J. Am. Chem. Soc.* **1959**, *81*, 5943. (c) Heasley, V. L.; Frye, C. L.; Gore, R. T.; Wilday, P. S. *J. Org. Chem.* **1968**, *33*, 2342. (d) Heasley, V. L.; Heasley, G. E.; Taylor, S. K.; Frye, C. L. *J. Org. Chem.* **1970**, *35*, 2967. The mechanistic details of the conversion of **9** to **10** as well as parameters such as reaction temperature, solvent, and $I^+$ source are currently under investigation and will be reported shortly.

(14) The use of other metal bromides gave poor yields of **12** and gave side products which included the corresponding pyrrolidine resulting from intramolecular displacement of the bromide in **12** by the amide.

(15) Dawe, R. D.; Molinski, T. F.; Turner, J. V. *Tetrahedron Lett.* **1984**, *25*, 2061.

(16) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.

(17) Zweifel, G.; Ayyangar, N. R.; Brown, H. C. *J. Am. Chem. Soc.* **1963**, *85*, 2072.

(18) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(19) Camarasa, M. J.; Fernández-Resa, P.; García-López, M. T.; De las Heras, F. G.; Méndez-Castrillón, P. P.; Felix, A. S. *Synthesis* **1984**, 509.

(20) Černý, M.; Staněk, J. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 23.

(21) Separation of the minor diastereomeric adduct (<3%) is effected at this stage; isolation and purification of **23** gives a single compound by $^1H$ and $^{13}C$ NMR spectroscopy.