Chemoenzymatic Synthesis of *trans*-4,5-Dihydroxycyclopent-2-enones: Conversion to D-1-Deoxynojirimycin

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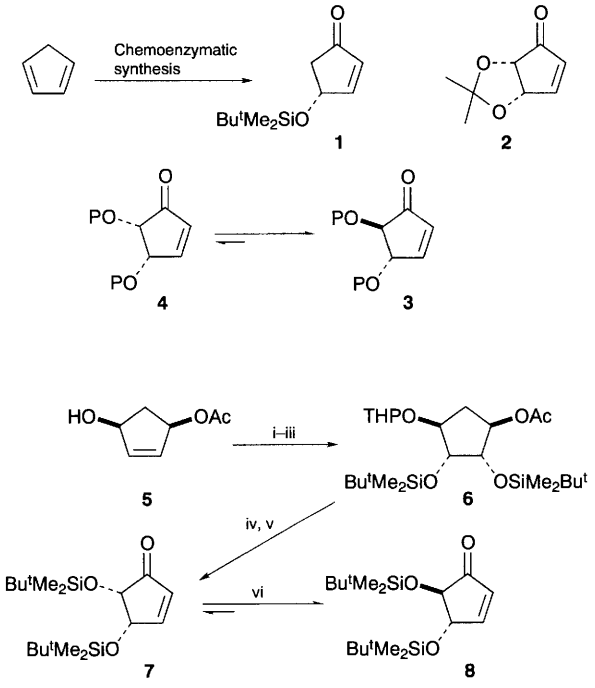
(4*R*,5*S*)-*trans*-4,5-Bis(*tert*-butyldimethylsilyloxy)cyclopent-2-enone **8** and (4*R*,5*S*)-*trans*-4,5-di(benzyloxy)cyclopent-2-enone **20** are prepared by equilibration of the corresponding *cis* derivatives; enone **8** is transformed into the glucosidase inhibitor, D-1-deoxynojirimycin **14**.

Chiral enones are versatile starting materials in the synthesis of target molecules[1] including sugars and related polyhydroxylated natural products.[2] Recently we described the use of enones **1** and **2** in the synthesis of a variety of aza-sugars, analogues of monosaccharides wherein the ring oxygen is replaced by nitrogen.[3] Deoxynojirimycin, stereochemically related to glucose and the best known molecule in this class, has potent biological activity associated with its ability, and that of its derivatives, to inhibit glucosidases.[4] We envisioned a synthesis of deoxynojirimycin *via* a chiral enone **3** with *trans* orientation of the ring oxygen substituents.

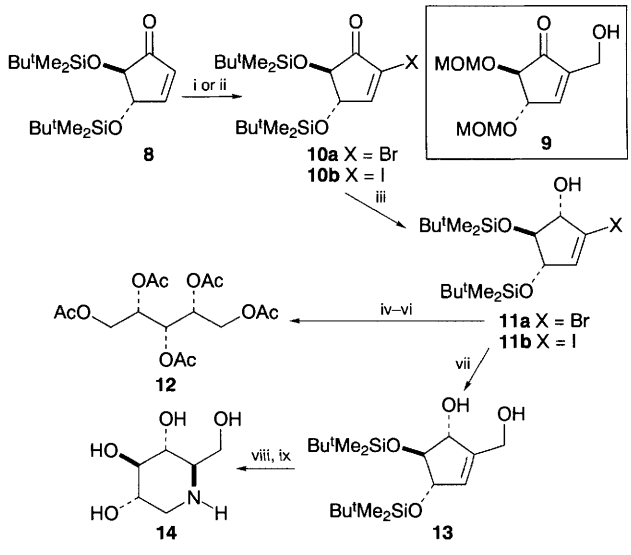
Enones **1** and **2** have been prepared by processes involving enzymatic asymmetrization of *meso*-diols or the corresponding diacetates derived from cyclopentadiene.[5] The synthesis of **2** is quite efficient, owing in part to the advantage gained by an enzymatic asymmetrization of a *meso* intermediate compared to an enzymatic resolution. For this reason it appeared to us that enones of type **3** might be best approached by a process involving epimerization of the corresponding *cis* derivative **4**. Previous work in this laboratory has demonstrated that a *cis*-α,β-dihydroxycycloalkanone can be readily isomerized to its *trans* counterpart upon simple exposure to silica gel if the appropriate hydroxy protecting groups are in place.[6]

THP protection† of optically active monoacetate **5**, followed by *cis*-hydroxylation and bis(silylation) of the resultant diol provided compound **6**. Removal of the tetrahydropyranyl protection followed by oxidation led to *cis*-enone **7**. Epimerization of enone **7** to enone **8** was achieved by treatment with DBU in dichloromethane (Scheme 1). Evidence of *trans* orientation of the silyoxy substituents in **8** was provided by comparison of the NMR data to a related literature compound **9** which had been prepared from glucose.[7] Enone **8** was converted to bromoketone **10a**, which was reduced with DIBAL-H to provide compound **11a** in admixture with its diastereoisomer (4 : 1). The two diastereoisomers were separated and the major **11a** was transformed to the known *meso*-xylitol pentaacetate (**12**)[8] establishing the stereochemistry of **11a** as shown (Scheme 2).

Enone **8** was iodinated,[9] using protocol established in our group, and then reduced to provide compound **11b** in good chemical yields. The key intermediate **13** was then achieved utilizing a Pd^0-mediated carbon monoxide coupling procedure.[10] Ozonolysis of this substrate followed by reductive animation[11] with sodium cyanoborohydride in MeOH provided a protected aza-sugar derivative which was then subsequently deprotected to provide D-1-deoxynojirimycin **14**. Both spectroscopic and optical data on this material were comparable to literature values.[11a] The synthetic interest in this substance has been high since its discovery and structure determination a quarter of a century ago.[12] Most syntheses have originated with natural chiral pool materials—glucose,[12,13a] mannose,[13b,c] pyroglutamic acid,[13d] tartaric acid[13f]—others utilized *myo*-inositol,[13c] and an aldolase-catalysed coupling of three-carbon sugar fragments.[13g] The present synthesis is unusual in that the six-carbon framework is derived from cyclopentadiene and carbon monoxide.



Scheme 1 *Reagents and conditions*: i, dihydropyran, pyridinium toluene-*p*-sulfonate, CH_2Cl_2, 96%; ii, OsO_4, 4-methylmorpholine *N*-oxide, THF, 92%; iii, Bu^{t}Me$_2$SiCl, imidazole, DMF, 85%; iv, $MgBr_2$, Et_2O, 75%; v, pyridinium dichromate, CH_2Cl_2 then Et_3N, 85%; vi, DBU, CH_2Cl_2, room temp., 60% based on recovered **7**

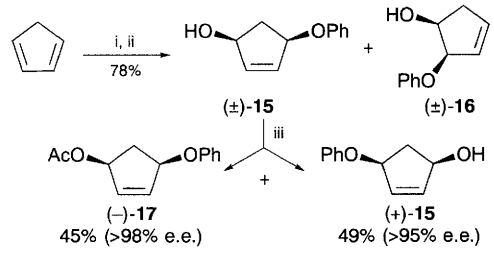


Scheme 2 *Reagents and conditions*: i, Br_2, CH_2Cl_2 then Et_3N, 83%; ii, I_2 (1.8 equiv.), pyridine–CCl_4, 91%; iii, DIBAL-H, Et_2O, −78 °C, 75% for **11a** and **11b**; iv, O_3, MeOH, −78 °C then Me_2S, 20 °C, 100%; v, $LiAlH_4$, THF then HCl, H_2O–MeOH, *ca.* 100%; vi, Ac_2O, pyridine, DMAP, room temp., 89%; vii, CO (1 atm), Bu_3SnH, $Pd(PPh_3)_4$ (5 mol%), THF; then $NaBH_4$, $CeCl_3·7H_2O$, MeOH, −78 °C, 50%; viii, O_3, MeOH, −78 °C followed by Me_2S then 1.5 equiv. $BuNH_3Cl$, 1.5 equiv. $NaCNBH_3$, MeOH, 25 °C, 55%; ix, HCl–MeOH then H_2, 30 psi, Pd–C, MeOH, 100%

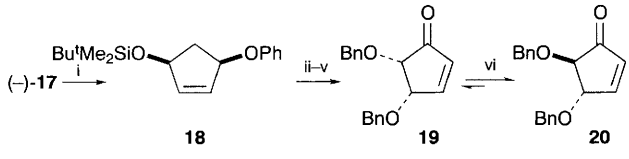
An alternative route for the production of a *trans* enone of type **3** was also investigated. The procedure reported by Siddiqi *et al.*[5d] to convert cyclopentadiene to the enantiopure enone **1**, *via Pseudomonas cepacia* lipase hydrolytic resolution of the acetate of (±)-**15**, attracted our attention. Cyclopentadiene was converted to the monoepoxide with peracetic acid. The monoepoxide in dichloromethane was treated with phenol in the presence of a catalytic amount of $(Ph_3P)_4Pd$ to give 65–80% of the *cis*-4-phenoxycyclopent-2-enol (±)-**15** and *ca.* 5% of *cis*-2-phenoxycyclopent-2-enol (±)-**16**. For large scale reactions (> 100 g) after aeration and filtration through a small plug of silica gel to remove Pd, the lower boiling **16** was separated by careful vacuum distillation to afford the clean (±)-**15** (Scheme 3).We carried out resolution of the racemic alcohol **15** in the synthesis direction with 10% *m/m* Amano PS-30 lipase (crude *Pseudomonas cepacia* lipase) in isopropenyl acetate–hexanes at 25–40 °C. When the reaction reached 50% conversion as determined by gas chromatography, the acetate and the residual alcohol each had an e.e. of > 95% (chiral HPLC, Chiralcel OB). A single recrystallization of the acetate (−)-**17** from hot hexanes yielded a product with e.e. 98%. Alcohol (+)-**15** was converted to ent-**17** which was purified to > 98% e.e. by recrystallization from hexanes.

Acetate (−)-**17** was converted to alcohol (−)-**15** with KOH–MeOH and then to **18** which was processed as described in Scheme 4 to *cis*-di(benzyloxy)ketone **19**. A 4:1 mixture of enones **20** and **19** was obtained by epimerization of **19** in the presence of Hunig's base in toluene at reflux. The major product **20** was isolated by chromatographic purification on silica gel (Scheme 4).

Enantiopure derivatives of the *cis*-4,5-dihydroxycyclopent-2-enone, *e.g.* **2**, have proved to be valuable starting materials for the synthesis of a variety of bioactive products including prostaglandins,[5b] carbocyclic nucleosides,[5c,d] and aza-sugars.[3a] Herein we have described the synthesis of two protected derivatives (**8** and **20**) of the corresponding *trans*-4,5-dihydroxycyclopent-2-enone by routes which, by modest alterations, could be adapted to provide compounds of enantiomeric series. Enone **8** was transformed to D-1-deoxynojirimyin. Similar enones have been utilized in the synthesis of trehazoline and related systems.[7] These enones could serve as precursors to neocarzinostatin and related compounds.[14]‡



Scheme 3 *Reagents and conditions*: i, $MeCO_3H$, Na_2CO_3; ii, $Pd(PPh_3)_4$, PhOH; iii, *Pseudomonas cepacia* lipase (Amano PS-30), isopropenyl acetate



Scheme 4 *Reagents and conditions*: i, KOH, MeOH then Bu^tMe_2SiCl, imidazole, DMF, 20 °C, 98%; ii, OsO_4, THF, 4-methylmorpholine *N*-oxide, room temp., 89%; iii, BnBr, NaH, DMF, room temp., 84%; iv, tetrabutylammonium fluoride, THF, 98%; v, pyridinium dichromate, molecular sieves, CH_2Cl_2 then pyridine overnight, 68%; vi, $Et_2(Pr^i)N$, toluene, 90 °C

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Footnotes

† The tetrahydropyranyl (THP) derivative was made to avoid mechanical problems in handling a triol in the subsequent OsO_4 oxidation step.

‡ *Selected physical data* for **7**: $[\alpha]_D^{25}$ +31.1 (*c* 1.1, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ −4.3, −4.5, −4.6, 18.3, 25.8, 25.9, 70.8, 73.6, 132.8, 159.2, 205.8. For **8**: $[\alpha]_D^{25}$ +102.9 (*c* 1.7, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ −5.1, −4.7, −4.3, 17.9, 18.3, 25.7, 25.7, 78.0, 82.7, 131.9. 159.2, 202.9. For **10**: $[\alpha]_D^{25}$ +84.2 (*c* 0.9, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ −5.1, −4.8, −4.7, −4.4, 17.9, 18.2, 25.7, 79.5, 80.3, 101.3. 165.1, 197.9. For **14**: mp 192 °C; $[\alpha]_D^{25}$ +42.5 (*c* 0.4, H_2O) {lit.[13] mp 196 °C; $[\alpha]_D^{25}$ +47 (*c* 1.0, H_2O)}; ^{13}C NMR (D_2O) δ 48.4, 60.4, 61.0, 70.5, 71.2, 78.2. For **17**: mp 74–75 °C; $[\alpha]_D^{20}$ −32.5 (*c* 1.0, acetone) {lit.[5d] mp 64–65 °C; $[\alpha]_D^{25}$ −32.5 (*c* 1.0, acetone)}. For *ent*-**17** [from (+)-**15**]: mp 73–75 °C; $[\alpha]_D^{20}$ +32.9 (*c* 1.0, acetone) {lit.[5d] mp 65–66 °C; $[\alpha]_D^{25}$ +32.3 (*c* 1.0, acetone)}. For **19**: $[\alpha]_D^{20}$ +22.1 (*c* 0.5, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 71.8, 72.3, 75.3, 76.0, 127.9, 128.1, 128.3, 128.4, 134.5, 137.4, 137.7, 158.9, 204.6. For **20**: $[\alpha]_D^{20}$ +61.7 (*c* 1.5, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 72.2, 72.8, 81.8, 83.8, 127.4, 128.0, 128.1, 128.3, 128.4, 128.5, 133.5, 137.3, 157.6, 203.3.

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