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Asymmetric synthesis of palitantin from the (5*R*)-*tert*-butyldimethylsiloxy-2-cyclohexenone

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Abstract

(+)-Palitantin (**2**) has been synthesized in 25% overall yield from the (5*R*)-*tert*-butyldimethylsiloxy-2-cyclohexenone [(*R*)-**1**] where a remarkable diastereoselective cat. OsO_4 *cis*-dihydroxylation of (*R*)-**1** furnished the precursor of the optically pure (5*R*,6*R*)-*bis*-trimethylsiloxy 2-cyclohexenone (**7**) which underwent highly selectively the 1,4-addition reaction of the 1,3-heptadienyl cyanocuprate to give, after trapping of the corresponding copper enolate with formaldehyde, the target compound.

Keywords: asymmetric synthesis; copper; copper compounds; cyclohexenones; hydroxylation.

We have recently reported the preparation of both enantiomers of the 5-*tert*-butyldimethylsiloxy-2-cyclohexenone, (*R*)- and (*S*)-**1**, and their reactions with organocopper reagents which, interestingly, enable the preparation of both diastereoisomers of the 1,4-adducts highly selectively by proper use of either lower- or higher-order cyanocuprates.[1] We have synthesized several natural products such as carvone, penienone and penihydrone from **1** which had been used as a chiral 2,5-cyclohexadienone synthon.[1c] We then turned our attention to palitantin (**2**) which appeared to be an attractive target for the further utilization of **1** in organic synthesis.

(+)-Palitantin (**2**), isolated from the *Penicillium Palitans*,[2] is a precursor of frequentin (**3**) which has shown antifungal and antibiotic activities.[3] So far, one racemic[4] and two enantioselective syntheses of **2** have been reported.[5,6] Our synthesis of the naturally occurring (+)-**2** was planned as illustrated in Scheme 1 which involves a stereoselective *cis*-dihydroxylation of (*R*)-**1**, conversion of the resulting *cis*-1,2-diol into the 5,6-disiloxy-2-cyclohexenone by elimination of the TBSO group after protection of the 1,2-diol moiety as silylethers and a stereoselective 1,4-addition of the (*E*,*E*)-1,3-heptadienylcuprate to it, followed by a trapping of the resulting copper enolate with formaldehyde. This retrosynthetic approach proved to be fruitful as shown in Scheme 2.

The *cis*-dihydroxylation of (*R*)-**1**, to our satisfaction, proceeded highly stereoselectively by catalytic osmium dihydroxylation (cat. OsO_4–NMO) to furnish the single diastereomer **4** in 80% yield, the

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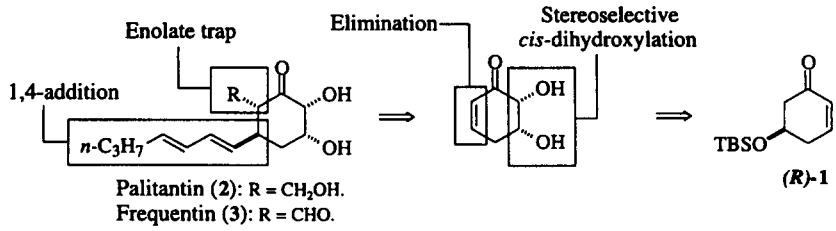
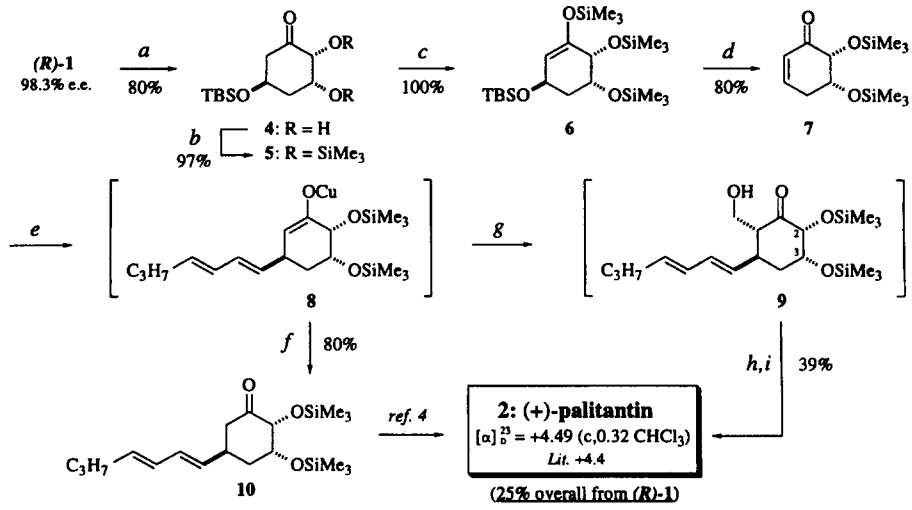


Scheme 1. Retrosynthetic analysis of **2** from (*R*)-**1**



Scheme 2. *Reagents and conditions*: (a) OsO_4 (5 mol%)–NMO (2.5 equiv.), acetone–H_2O, rt, 24 h; (b) BSA (3 equiv.), CH_3CN, rt, 15 h; (c) LiHMDS (2 equiv.), TMEDA (2.5 equiv.), toluene–C_6H_{14}, −78°C→rt→−78°C then TMSCl (2 equiv.), and **5** in toluene were added over a period of 1 h, stirred for 2 h at −78°C, then addition of Et_3N and work-up; (d) dry-TBAF (5 mol%), 4 Å MS, THF, −30°C, 5 min; (e) hept-3-ene-1-yne/$Cp_2Zr(H)Cl$, THF, rt 15 min then MeLi (3 equiv.), −78°C, 10 min then CuCN·2LiCl, −78°C, then (*R*)-**1**, −78°C, 40 min; (f) sat. NH_4Cl. (g) CH_2O/Et_2O, −78°C, 1 h and sat. NH_4Cl. (h) 1N citric acid/MeOH, rt, 10 min; (i) DBU (3 equiv.), CH_2Cl_2, rt, 4 h. Abbreviations: BSA=bis-(trimethylsilyl)acetamide; DBU=1,8-diazabicyclo[5.4.0]undec-7-ene; LiHMDS=lithium bis(trimethylsilyl)amide; MS=molecular sieves; NMO=4-methylmorpholine *N*-oxide; TBAF=tetrabutylammonium fluoride; TMEDA=*N*,*N*,*N*′,*N*′-tetramethylethylenediamine

stereochemistry of which had been assigned after completion of the total synthesis.[7] Bearing in mind the detailed study of Hanessian et al. on the regioselective enolization of a 2,3-(trimethylsiloxy)-5-substituted cyclohexanone,[5] we protected the *cis*-1,2-diol **4** as the corresponding *bis*-trimethylsilyl ether **5**, which was obtained as a white crystalline product. Then, the desiloxylation of **5** into **7** was first carried out with LiHMDS/hexane in the presence of TMEDA at −78°C in toluene. The reaction, however, resulted in a steady recovery of **5** in 50% yield with production of **7** in about 35% yield (73% yield based on the consumed **5**) and our efforts aiming at improving this yield by changing the reaction conditions (base, solvent, temperature and/or reaction time) did not meet with much success. We, therefore, searched for other conditions and finally achieved a satisfactory result through the conversion of **5** into the trimethylsilylenol ether **6** quantitatively (TMSCl–internal quench)[8] and the following transformation into **7** in 80% yield upon treatment with catalytic dry-TBAF (5 mol%).[9] With **7** in hand, the synthesis of **2** was completed as follows: the 1,4-addition reaction of the higher-order (*E*,*E*)-1,3-heptadienyl cyanocuprate (prepared via hydrozirconation of the (*E*)-hept-3-ene-1-yne and transmetallation with $Me_2Cu(CN)Li_2$)[1c,10] onto **7** proceeded highly selectively in a *trans*-fashion to yield, after hydrolysis,

10 in 80% yield as a single diastereoisomer. The adduct **10** had been synthesized by Hanessian et al.[5] as the precursor of **2**: the proton NMR spectrum as well as the $[\alpha]_D$ value of the compound obtained here[11] are well coincident with the ones reported.[5] Nevertheless, we tried to trap the copper enolate (**8**) with formaldehyde in order to reach **2** directly: the reaction gave, after work-up, a rather complex mixture consisting of **9** and its partially desilylated products at C2 and C3 and possibly their epimers (judged by proton NMR of the crude product). The crude reaction mixture was then treated with 2N H_2SO_4/MeOH or 1N citric acid/MeOH to give, after column chromatography, the expected product **2** and a considerable amount of an epimer (from 10 to 20%); treatment of the corresponding mixture with DBU at rt cleanly afforded the desired **2**. Thus, **2** was obtained in a modest 39% overall yield from **7**.[11]

In conclusion, we have synthesized (+)-palitantin in a straightforward and efficient process from (*R*)-**1** (six steps, 25% overall yield). The discovery of the highly diastereoselective *cis*-dihydroxylation of a 5-siloxy-2-cyclohexenone which, to the best of our knowledge, has not been reported in the literature, prompted us to investigate the dihydroxylation of a variety of 5-substituted 2-cyclohexenones, the results of which will be reported in due course.

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(dd, J=3.9, 1.5 Hz, 1H), 3.82 (br s, 1H), 2.80 (ddd, J=13.5, 5.1, 2.7 Hz, 1H), 2.60 (br s, 1H), 2.46 (ddd, J=13.5, 10.5, 1.2 Hz, 1H), 2.39 (dddd, J=14.1, 4.2, 4.2, 2.7 Hz, 1H), 1.85 (ddd, J=14.1, 10.8, 2.4 Hz, 1H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR: δ 207.6, 77.0, 69.3, 66.9, 48.8, 38.5, 25.5, 17.8, −5.1. Compound **5** (white solid): mp 39°C; $[\alpha]_D^{23}$=+19.66 (*c* 0.72 $CHCl_3$); ^{1}H NMR: δ 4.30 (dddd, J=4.2, 4.2, 4.2, 4.2 Hz, 1H), 4.14 (ddd, J=6.0, 3.0, 3.0 Hz, 1H), 4.08 (d, J=2.7 Hz, 1H), 2.74 (ddd, J=13.5, 4.8, 1.8 Hz, 1H), 2.29 (dd, J=12.9, 8.4 Hz, 1H), 2.20–2.09 (m, 1H), 1.79 (ddd, J=13.2, 8.4, 2.7 Hz, 1H), 0.86 (s, 9H), 0.11 (s, 9H), 0.08 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR: δ 206.1, 79.3, 71.3, 66.7, 48.1, 39.9, 25.6, 17.9, 0.1, 0.0, −5.0, −5.1. Compound **7** (low melting point solid): $[\alpha]_D^{23}$=−3.98 (*c* 0.71 $CHCl_3$); ^{1}H NMR: δ 6.75 (dddd, J=10.2, 3.9, 3.9, 0.9 Hz, 1H), 6.01 (ddd, J=10.2, 1.8, 1.8 Hz, 1H), 4.24–4.18 (m, 2H), 2.59 (dd, J=3.9, 1.8 Hz, 1H), 2.57 (dd, J=3.9, 1.8 Hz, 1H), 0.15 (s, 9H), 0.08 (s, 9H); ^{13}C NMR: δ 197.7, 145.4, 128.4, 77.7, 72.8, 34.3, 0.17, 0.14. Compound **10** (oil): $[\alpha]_D^{23}$=+40.4 (*c* 0.18 $CHCl_3$) [Lit. +41.2 (*c* 1.09 $CHCl_3$)]; ^{13}C NMR: δ 206.8, 134.1, 133.9, 130.0, 129.7, 79.0, 74.5, 45.8, 38.4, 35.6, 34.6, 22.3, 13.6, 0.2, 0.1.