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An Efficient Catalytic Stereoselective Route to a Key Intermediate for the Synthesis of the Long-Lived PGI_2 Analog ZK 96480 (Cicaprost™)

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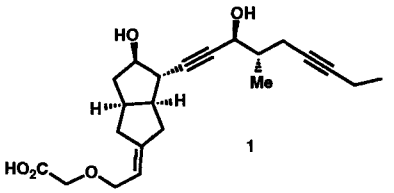
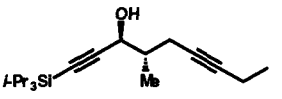
Summary: *An expeditious and stereoselective synthesis of a key chiral intermediate (2) for the synthesis of the therapeutically useful PGI_2 analog Cicaprost™ is described.*

Primary pulmonary hypertension (PPH) is an increasingly common and fatal disease. The only life-sustaining treatments for PPH at present are either 24-hour infusion therapy with prostaglandin I_2 (PGI_2) or combined heart-lung transplant.[1] Long lived, metabolically stable, and orally active PGI_2 analogs such as Cicaprost™ (**1**)[2] (dose 0.5 mg/kg, $t_{1/2}$ ca. 1 h), offer the prospect of a far more acceptable dosing regimen for the first option.[3,4] Unfortunately, published syntheses of Cicaprost are long and possibly impractical.[5] Described herein is a simple and efficient synthetic route to the key intermediate **2** which corresponds to the omega-sidechain of Cicaprost.



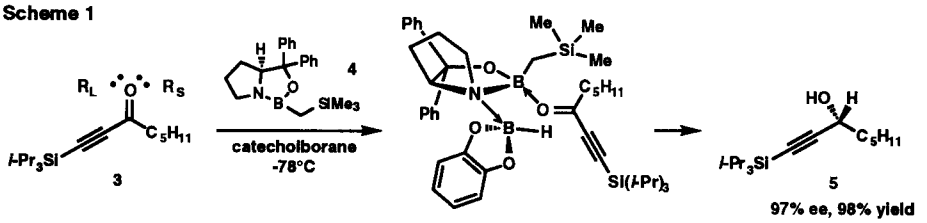
1



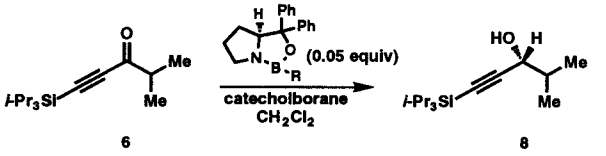
2

We have recently reported a highly enantioselective catalytic reduction of α,β-ynones to propargylic alcohols as shown in Scheme 1.[6,7] For example, treatment of ketone **3** and oxazaborolidine **4** (0.05 equiv) with catecholborane (1.2 equiv) in CH_2Cl_2 at -78 °C produced the (*R*)-acetylenic alcohol **5** in 97% enantiomeric excess (ee) and 98% yield. The high level of asymmetric induction observed in this process is the result of a repulsive long range steric interaction between the terminal triisopropylsilyl group and the bulky trimethylsilylmethyl substituent on the boron atom of the catalyst, thus favoring binding of the catalyst to the ketone electron lone pair *anti* to the triisopropylsilylalkynyl substituent. As a result, the triisopropylsilylalkynyl substituent functions as the larger group (R_L) versus the *n*-pentyl group (R_S).

Scheme 1



The effectiveness of this methodology led us to study the reduction of isopropyl ketone **6** to alcohol **8** as a model for the preparation of **2**. Utilization of (*S*)-B-CH_2SiMe_3 catalyst **4** at -78 °C provided **8** in only 72% ee. (*S*)-B-*n*-Bu catalyst **7**, however, resulted in a substantial improvement in enantioselectivity to 90% ee.[6,8] A further increase to 97% ee was obtained by (1) performing the reduction at -60 °C, and (2) pre-cooling the CH_2Cl_2 solution of catecholborane by slow addition down the side of the flask.[9,10]



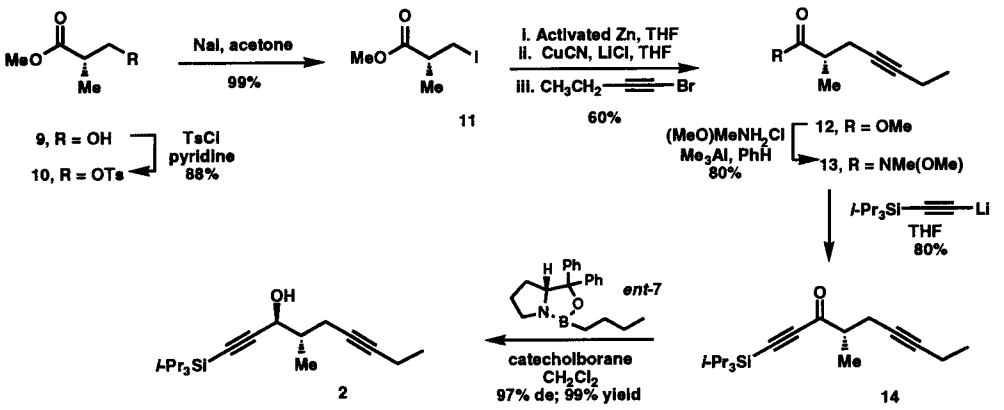
Catalyst	Enantiomeric Excess (%)	T (°C)
4 (R=CH_2SiMe_3)	72	-78
7 (R=*n*-Bu)	90	-78
7	97	-60

These optimized conditions are ideally suited to the stereoselective synthesis of omega-sidechain **2** as outlined in Scheme 2. Treatment of methyl-(*S*)-(+)-3-hydroxy-2-methylpropionate (**9**)[11] and 7 equiv of pyridine at 0 °C with 1.3 equiv of *p*-toluenesulfonyl chloride for 10.5 h provided tosylate **10** (88%), which was converted to known iodide **11** under Finkelstein conditions (NaI, acetone, 60 °C, 2 h, 99% yield).[12,13] Iodide **11** and 3 equiv of activated zinc dust[14] in THF were heated at 40 °C for 4 h.[15] The resulting organozinc reagent was added to 0.9 equiv of copper(I) cyanide and 1.8 equiv of LiCl in THF at -10 °C, stirred 10 min, cooled to -78 °C, treated with 1-bromo-1-butyne,[16] and warmed to -60 °C for 20 h to provide alkynyl ester **12** in 60% yield.[13,17] *N,O*-Dimethylhydroxylamine hydrochloride (3 equiv) in benzene at 0 °C was treated with 3 equiv of Me_3Al (2 M in hexanes), and stirred 1 h.[18] Alkynyl ester **12** (1 equiv) was added and the solution was heated at 50 °C for 3 h. The reaction was quenched by the addition of MeOH, diluted with CH_2Cl_2, stirred with Na_2SO_4-$10H_2O$ (9 equiv), and filtered to afford after silica gel chromatography Weinreb amide **13** in 80% yield, $[\alpha]_D^{23}$ +6.9 (*c* 1.3, CH_2Cl_2). Lithium triisopropylsilylacetylide (1.3 equiv of triisopropylsilylacetylene[19], 1.2 equiv of *n*-BuLi, THF, -78 °C to 0 °C, 30 min) was added to a solution of **13** in THF at -10 °C. After 30 min the reaction was quenched with saturated NH_4Cl solution to give ketone **14** in 80% yield, $[\alpha]_D^{23}$ -10.2 (*c* 1.3, CH_2Cl_2). To a solution of **14** and 0.05 equiv of (*R*)-B-*n*-Bu catalyst *ent*-**7** in CH_2Cl_2 at -60 °C was added 1.2 equiv of catecholborane in CH_2Cl_2 which afforded, after 3 h, alcohol **2** in 97% diastereomeric excess (de) and 99% yield,

$[\alpha]_D^{23}$ +40.8 (*c* 1.75, CH_2Cl_2).[20,21] Utilization of catalyst **7** in the reduction of **14** produced the other diastereomer in 96% de and 99% yield, ($[\alpha]_D^{23}$ -6.4 (*c* 0.55, CH_2Cl_2)), demonstrating that the reduction of chiral ketone **14** is a reagent-controlled process.

The stereoselective preparation of **2** described herein proceeds in 6 steps and 33% overall yield starting from readily available methyl-(*S*)-(+)-3-hydroxy-2-methylpropionate (**9**). This synthesis highlights an effective carbon-carbon bond formation utilizing an enantiopure homoenolate for the rapid construction of requisite ketone **14** and a practical application of long range steric effects in the chiral oxazaborolidine-catalyzed reduction of ketones.[22]

Scheme 2



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8. For the preparation of **7** see: Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1996**, *37*, 4837.

9. The absolute stereochemistry of **8** was determined to be *R* by (1) benzoylation (BzCl, 4-(dimethylamino)pyridine (DMAP), Et_3N, CH_2Cl_2, 97% yield), (2) alkyne oxidation to the carboxylic acid ($RuCl_3$ (cat), $NaIO_4$, CH_3CN, CCl_4, H_2O, 66% yield), and (3) thioesterification (ClC(O)OEt, Et_3N, CH_2Cl_2, 0 °C; EtSH, DMAP, 74% yield) to provide *S*-ethyl-(*R*)-2-(benzoyloxy)-3-methylthiobutyrate: $[\alpha]_D^{23}$ -17.4 (*c* 1.75, $CHCl_3$), lit. for (*S*)-isomer $[\alpha]_D^{23}$ +18.9 (*c* 0.94, $CHCl_3$). See: Falck, J. R.; Bhatt, R. K.; Ye, J. *J. Am. Chem. Soc.* **1995**, *117*, 5973.
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19. Triisopropylsilylacetylene was prepared via the reaction between lithium acetylide and triisopropylsilyl chloride. See: Bottaro, J. C.; Hanson, R. N.; Seitz, D. E. *J. Org. Chem.* **1981**, *46*, 5221.
20. Reduction of **14:** Ketone **14** (45 mg, 0.148 mmol, azeotropically dried with toluene) was treated with (*R*)-B-*n*-Bu catalyst *ent*-**7** (74 µL, 0.007 mmol, 0.1 M solution in toluene). Toluene was removed *in vacuo*, CH_2Cl_2 (900 µL) was added, the solution was cooled to -60 °C, and catecholborane (23 mg, 20 µL, 0.192 mmol) in CH_2Cl_2 (142 µL) was added down the side of the flask over 10 min. After 3 h, MeOH (200 µL) was added, the solution was warmed to room temperature, diluted with hexanes (3 mL), and applied directly to a silica gel column for purification (hexanes to 10:1 hexanes-Et_2O). This provided 45 mg (>99% yield) of **2** as a clear oil; $[\alpha]_D^{23}$ +40.8 (*c* 1.75, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 4.41 (t, J=5.6 Hz, 1H), 2.28 (m, 2H), 2.16 (qt, J=2.2, 7.5 Hz, 2H), 1.93 (m, 2H), 1.12 (m, 5H), 1.07 (d, J=2.7 Hz, 21H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.021, 86.769, 83.409, 66.524, 39.259, 22.324, 18.609, 14.952, 14.311, 12.458, 11.199 ppm; FT-IR (neat) 3400, 2960, 2943, 2893, 2866, 883 cm^{-1}; MS (CI): 324 ($[M+NH_4]^+$, 100); HRMS (CI): calcd for $[C_{19}H_{34}OSi + NH_4]^+$: 324.2723; found: 324.2736. Conversion of the alcohols to the *p*-nitrobenzoates (*p*-nitrobenzoylchloride, DMAP, CH_2Cl_2, 23 °C) and HPLC analysis (Chiralcel OD, 0.25% *i*-PrOH in hexanes, 0.6 mL/min, λ=235 nm) showed the product to be of 97% de (R_t: 29.8 min, major; 35.6 min, minor).
21. The relative stereochemistry of the reduction of ketone **14** to alcohol **2** was assigned by analogy with the reduction of ketone **6** to alcohol **8**.
22. This research was supported by grants from the National Institutes of Health and the National Science Foundation.

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