Tetrahedron Letters, Vol.32, No.41, pp 5713-5716, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

Enantioselective Route to α-Hydroxy Aldehyde and Acid Derivatives

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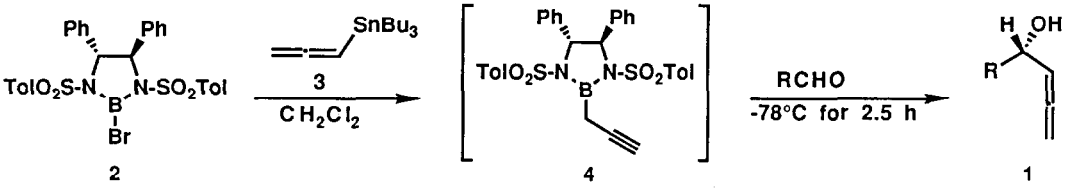
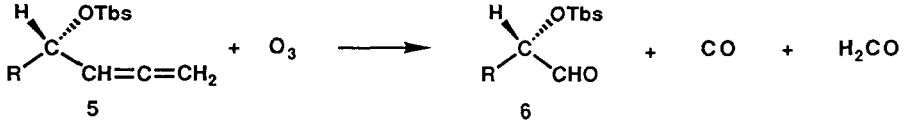
Summary: Methodology is described for the enantioselective synthesis of chiral O-protected α-hydroxy aldehydes, acids and esters from achiral aldehydes having one less carbon.

An enantioselective conversion of aldehydes to chiral propa-1,2-dienyl carbinols **1** has recently been developed in these laboratories based on the reaction of the chiral bromoborane **2** and 1,2-propadienyltributylstannane (**3**) to generate the chiral reagent **4**.[1] This one-step process is highly enantioselective and allows ready access to a wide variety of carbinols **1** with >99% enantiopurity.[1] In this note we demonstrate that these chiral propa-1,2-dienyl carbinols can be used to produce versatile synthetic intermediates such as chiral α-hydroxy aldehyde and acid derivatives.



2 **4** **1**

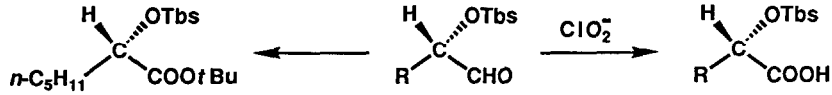
The reaction of an allene with one equivalent of ozone, as first described by Favorskii[2] and investigated in detail by Kolsacker,[3] usually trisects the allene function to give CO from the central carbon, and ketone or aldehyde products from the remaining carbons. As applied to a *tert*-butyldimethylsilyl (Tbs) derivative **5** of a propa-1,2-dienyl carbinol **1**, this oxidation is expected to generate the Tbs ether of an α-hydroxy aldehyde (**6**).



5 **6**

Indeed, for three test substrates, R = *n*-C_5H_{11}, R = C_6H_5 and R = *t*-Bu, the Favorskii ozonolysis proceeds very cleanly (CH_2Cl_2 solution at -78 °C) to form the silylated chiral α-hydroxy aldehydes **6** in 89-99% yield. Ozone was passed into a cold solution of the allene **5** until a slight violet color persisted, the solution was purged with N_2 and concentrated *in vacuo* to afford essentially pure chiral aldehyde **6** (by tlc and 500 MHz ^1H NMR analysis). Oxidation of the α-silyloxy aldehydes either to the corresponding free acid or *tert*-butyl ester was readily accomplished. Thus, when **6**, R = *n*-C_5H_{11},[4] was treated with 10 equiv of sodium chlorite in water-*tert*-

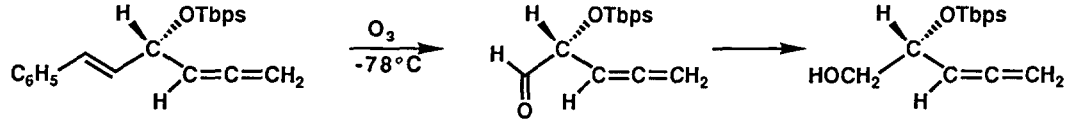
butyl alcohol in the presence of sodium dihydrogen phosphate and trimethylethylene at 23 °C for 25 min, the Tbs derivative of (*S*)-2-hydroxyheptanoic acid (**7**)[5,6] was formed (79% isolated yield after extractive isolation and purification by silica gel chromatography using 4 : 1 hexane–ether containing 1% HOAc for elution). Desilylation of **7** (aq. HF-pyridine, CH_3CN, 23 °C, 1 h) afforded the known 2-hydroxy heptanoic acid (94%). Reaction of **6**, R = *n*-C_5H_{11}, with $CrO_3 \bullet (pyridine)_2$ in CH_2Cl_2–DMF (4 : 1) at 23 °C for 10 min



8 **6, R = *n*-C_5H_{11}** **7**

followed by addition of 13 equiv of Ac_2O and 32 equiv of *t*-BuOH and reaction at 23 °C for 16 h produced *tert*-butyl ester **8**[7] in 67% yield after isolation by the sequence: (1) quenching of excess CrO_3 by addition of a little ethanol, (2) addition of EtOAc and filtration through layers of sodium sulfate (top) and silica gel, (3) concentration *in vacuo*, and (4) silica gel chromatography using 7 : 3 hexane–ether as eluent.[8] In a parallel way the α-silyloxy aldehyde **6**, R = C_6H_5, was transformed into the *tert*-butyl ester of (*S*)-O-*tert*-butyldimethylsilyl mandelic acid (71% yield, $[\alpha]_D^{23}$ + 30° (c = 0.5 $CHCl_3$)).

The Favorskii ozonolysis of allenes, though complete in 5-10 min at -78 °C in CH_2Cl_2, is slower than the ozonolysis of ethylenic double bonds as is indicated by experiments with the chiral propa-1,2-dienyl silyl ether **9**. The reaction of 1 equiv of ozone with the *tert*-butyldiphenylsilyl (Tbps) ether **9** at -78 °C occurs



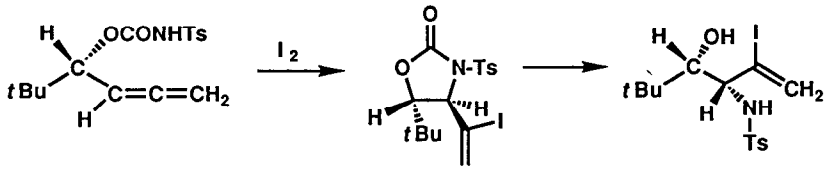
9 **10** **11**

selectively at the styryl unit to give the very sensitive allenic aldehyde **10**, which was isolated after ozonide reduction (Me_2S, MeOH, -78 °C, 30 min) and removal of solvent *in vacuo* and identified by ^1H NMR analysis.[9] Reduction of the same ozonide with sodium borohydride in methanol at -78 °C afforded cleanly (*R*)-2-*tert*-butyldimethylsilyloxy-penta-3,4-dien-1-ol (**11**).

1, R = *n*-C_5H_{11} **12**

There are a number of other transformations of chiral propa-1,2-dienyl carbinols which take advantage of the unique chemistry of this system to produce a variety of useful structures. Reaction of **1**, R = *n*-C_5H_{11}, with 0.2 equiv of silver nitrate in 3 : 2 acetone–water in the presence of calcium carbonate at 23 °C for 48 h resulted in

formation of the chiral dihydrofuran **12**,[10] $[\alpha]_D^{23}$ + 147° (c = 0.4, $CHCl_3$), in 81% yield after silica gel chromatography (3 : 1 hexane–ether as eluent).[11] In a different example, the chiral propa-1,2-dienyl carbinol **1**, R = *tert*-Bu, was converted into carbamate **13** (tosyl isocyanate–CH_2Cl_2, 23 °C, 1 h, 89%) which was transformed stereospecifically into the chiral 1,3-oxazolidine-2-one **14**,[12] $[\alpha]_D^{23}$ - 6.1° (c = 0.5, $CHCl_3$), in 79% yield by reaction with I_2–K_2CO_3 in dry ether at 23 °C for 24 h.[13] Reaction of **14** with KOH–THF (generated from KO*t*Bu–THF + H_2O) at 25 °C provided alcohol **15**.[13]



13 **14** **15**

The following experimental procedure is illustrative.

Silyl Ether 5, R = *n*-C_5H_{11}. (*R,R*)-1,2-*p*-toluenesulfonamido-1,2-diphenylethane[14] (2.65 g, 5.085 mmol) was placed in a flame-dried, 200 ml-flask under argon and dissolved in dry dichloromethane (30 ml). The resulting solution was cooled to 0 °C and treated with boron tribromide (1M, in dichloromethane, 4.88 ml, 4.88 mmol). After stirring at 0 °C for 10 min, and 25 °C for 50 min, the solution was concentrated to dryness at 1 mm Hg vacuum with exclusion of moisture by a NaOH/$CaSO_4$ trap. Dichloromethane (30 ml) was added, and the mixture was evaporated again. The residue was dissolved in dichloromethane (30 ml), the solution was cooled to 0 °C, and treated with a solution of stannyl allene **3**[1] (1.53 g, 4.67 mmol) in dichloromethane (6 ml) over 30 min. The solution was stirred at 0 °C for 4 h, then at 25 °C for 0.5 h, before cooling to -78 °C and dropwise addition of a solution of hexanal (0.522 ml, 4.32 mmol) in dichloromethane (6 ml). After 2 h, pH 7 phosphate buffer (30 ml) was added, and the mixture was warmed to room temperature. The aqueous layer was extracted with dichloromethane (10 ml), then the combined organic layers were dried and concentrated. The residue was dissolved in ether–hexane 3 : 1 (30 ml), then the solution was cooled to 0 °C. After 30 min, the resulting precipitate of recyclable bis sulfonamide (2.6 g) was collected. The filtrate was stirred with KF solution (50%, 90 ml) for 15 min, then separated. The organic layer was dried over potassium carbonate, filtered and condensed. SGC (1 : 9 ether–hexane as eluent) gave the allenic alcohol **1**, R = *n*-C_5H_{11}, as a clear oil (0.495 g, 82%). (Analysis of the MPTA derivative showed >99% ee). ^1H NMR ($CDCl_3$, 300 MHz), δ 0.9 (m, 3H), 1.23 - 1.68 (m, 8H), 4.16 (m, 1H), 4.85 (d, J = 6Hz, 1H), 4.86 (d, J = 6Hz, 1H) and 5.24 (dd, J = 6Hz, 6Hz, 1H); $[\alpha]_D^{23}$ + 4.5° (c = 0.2 $CHCl_3$).

The alcohol **1**, R = *n*-C_5H_{11}, (0.300 g, 2.14 mmol) was dissolved in dichloromethane (10 ml) and cooled to 0 °C. 2,6-Lutidine (0.504 ml, 4.32 mmol) was added, followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.590 ml, 2.57 mmol). The reaction mixture was stirred at 0 °C for 1 h, then warmed to room temperature. Sodium hydroxide (2N, 2 ml) was added and the mixture was diluted with dichloromethane (20 ml). The organic layer was washed with HCl (2N, 2 x 20 ml), brine (1 x 10 ml), then dried over magnesium sulfate. Filtration followed by SGC of the crude product (99 : 1 hexane–ether as eluent)

gave pure **5**, R = *n*-C_5H_{11}, as an oil (0.498 g, 92%). ^1H NMR ($CDCl_3$, 500 MHz): 0.09 (s, 6H), 0.90 (s, 12H), 1.29 - 160 (m, 8H), 4.10 (m, 1H), 4.70 (m, 2H), and 5.09 (dd, 1H, J=8 Hz, 8Hz); MS (CI) 255 (M+H).

Ozonolysis of 5, R = *n*-C_5H_{11}. Alcohol **5**, R = *n*-C_5H_{11}, (0.493 g, 1.94 mmol) was dissolved in dichloromethane (50 ml) and the solution was cooled to -78 °C. Ozone was bubbled through the solution until a faint violet color persisted in the solution. The solvent was removed *in vacuo* to give aldehyde **6**, R= *n*-C_5H_{11}, (0.468 g, 98%). ^1H NMR ($CDCl_3$ at 500 MHz), 0.10 (s, 6H), 0.90 (s, 12H), 1.25 - 1.65 (m, 8H), 3.95 (dt, J = 6.25Hz, 2.5Hz, 1H), 9.60 (d, J = 2.5Hz, 1H); $[\alpha]_D^{23}$ - 32° (c = 0.15, $CHCl_3$); MS (CI), 245 (M^+ + H); IR (neat), 1742 cm^{-1}.

The methodology reported herein is noteworthy for several reasons: (1) either the chiral allenes **1** or their enantiomers can be made since chiral bromoborane **2** and its enantiomer are equally readily available, (2) the chiral bis sulfonamide from which bromoborane **2** is derived can be recovered in >95% yield from the synthesis of **1** and recycled indefinitely, (3) the Favorskii ozonolysis of **5** → **6** is clean and the products are easily isolated, (4) O-protected α-hydroxy aldehydes and acids are versatile synthetic intermediates.[15]

References and Notes

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2. Favorskii, A. E.; Bone, M. D. *Dokl. Akad. Nauk. USSR* **1937**, *14*, 499; *Chem. Abstr.* **1937**, *31*, 5752.
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6. Found for **7**: ^1H NMR ($CDCl_3$ at 500 MHz), δ 0.10 (s, 6H), 0.95 (s, 9H), 1.30 (m, 9H), 1.77 (m, 2H) and 4.29 (t, J=6Hz, 1H); $[\alpha]_D^{23}$ - 2.6° (c = 1, $CHCl_3$); MS (CI), 259 (M^+ + H); colorless oil.[5a]
7. See, Corey, E. J.; Samuelsson, B. *J. Org. Chem.* **1984**, *49*, 4735.
8. Found for **8**: ^1H NMR ($CDCl_3$ at 250 MHz), δ 0.02 (s, 3H), 0.06 (s, 3H), 0.88 (m, 3H), 0.90 (s, 9H), 1.23 - 1.69 (m, 8H), 1.48 (s, 9H), 4.03 (t, J=6Hz, 1H); $[\alpha]_D^{23}$ - 26° (c = 0.4, $CHCl_3$), MS (FAB), 339 (M^+ + Na), IR (neat), 2955, 2929, 2857, 1749, 1138 cm^{-1}; colorless oil.
9. The *tert*-butyldiphenyl silyl (Tbps) protecting group is advantageous in this case for ease of isolation of the products **10** and **11**. Found for **10**: ^1H NMR ($CDCl_3$ at 400 MHz), 1.08 (s, 9H), 4.52 (m, 1H), 4.78 (dt, J=7Hz, 2Hz, 2H), 5.12 (dd, J=7Hz, 7Hz, 1H), 7.3 - 7.7 (m, 10H), 9.55 (s, 1H); MS (CI), 337 (M^+ + H); IR (neat), 2958, 2930, 2857, 2396, 2385, 1952, 1746, 1450, 700 cm^{-1}.
10. ^1H NMR (250 MHz, $CDCl_3$): 0.9 (t, J=7Hz, 3H), 1.2 - 1.6 (m, 8H), 4.61 (m, 2H), 4.82 (m, 1H), 5.78 (m, 1H), 5.88 (m, 1H); MS (CI), 141 (M^+ + H).
11. See, Marshall, J. A.; Wang, X-j. *J. Org. Chem.* **1990**, *55*, 2995.
12. Found for **14**: ^1H NMR (250 MHz, $CDCl_3$), 1.00 (s, 9H), 2.50 (s, 3H), 3.84 (d, J=2.6Hz, 1H), 4.55 (d, J=2.6Hz, 1H), 6.02 (d, J=3Hz, 1H), 6.58 (d, J=3Hz, 1H), 7.38 (d, J=8Hz, 2H), 7.98 (d, J=8Hz, 2H); IR, 1763 cm^{-1}; MS 450 (M^+ + H); $[\alpha]_D^{23}$ - 6.1° (c = 0.5, $CHCl_3$).
13. See, Friesen, R. W. *Tetrahedron Letters* **1990**, *31*, 4249.
14. (a) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493. (b) Pikul, S.; Corey, E. J. *Org. Synth.*, in press.

15. This research was supported by grants from the National Institutes of Health, the National Science Foundation, and SERC-NATO.

(Received in USA 18 July 1991)