Application of chiral 2-isoxazoline for the synthesis of syn-1,3-diol analogs

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Abstract
The asymmetric cycloaddition of TIPS nitronate catalyzed by “Cu(II)-bisoxazoline” gave the 2-isoxazoline product in 95% yield, which was converted into tert-butyl (3S,5R)-6-hydroxy-3,5-O-isopropylidene-3,5-dihydroxyhexanoate in 14 steps through a β-hydroxy ketone.

Introduction
The chiral 1,3-diol structure is widespread in a broad spectrum of natural products [1,2]. (3R)-β-Hydroxy-δ-lactone or its opening equivalent (3R)-syn-3,5-dihydroxypentanoic acid, is a common structure in naturally occurring mevastatin (or compactin), lovastatin or closely related statins, and synthetic statins. Either the syn or anti-1,3-diol could be prepared from enantiomerically pure β-hydroxy ketones through β-hydroxy-directed carbonyl reduction following Evans’ [3] or Prasad’s [4-11] method. The Narasaka–Prasad reduction of a δ-hydroxy-β-keto esters derived from β-hydroxy esters [12-23] is widely used to prepare tert-butyl (3R)-3,5-O-isopropylidene-3,5-dihydroxyhexanoate (Scheme 1a) [24-37], which is a building block for synthetic statins [38-41], though enzymatic syntheses [42-48] of the chiral β-hydroxy-δ-lactone moiety or its equivalents, pioneered by Wong [42], is equally competitive. Here, we report the preparations of tert-butyl (3S,5R)-6-hydroxy-3,5-O-isopropylidene-3,5-dihydroxyhexanoate and related syn-1,3-diol analogs from a chiral 2-isoxazoline (Scheme 1b). This work is part of our continuous efforts in asymmetric syntheses and applications of chiral 2-isoxazolines [49-51].

Results and Discussion
Our synthesis commenced with a chiral 3,5-disubstituted-2-isoxazoline 3 or 4, which were prepared from silyl nitronate through an asymmetric 1,3-dipolar cycloaddition developed in our lab (Table 1) [49]. The synthesis of the trisopropylsilyl nitronate was initially attempted starting with 3-nitropropionic acid methyl ester but no desired product was observed. How-
ever, switching to 3-nitropropanol, protected as the THP ether, succeeded to prepare the required triisopropylsilyl nitronate. Then, the catalytic asymmetric cycloaddition gave the 2-isoxazolidine cycloadduct 1 in a high yield. In the light of our previous ligand screening results [49], two bisoxazolines with an isopropyl (ligand B) or tert-butyl group (ligand A) were tested. Optimization of the conditions established that 26 mol % of ligand B together with 20 mol % Cu(OTf)$_2$ in anhydrous...
CH$_2$Cl$_2$ catalyzed the cycloaddition between N-acryloyl-1,3-oxazolidin-2-one and the silyl nitronate at −50 °C to give 1 in 95% isolated yield, which subsequently generated 3,5-disubstituted isoxazoline 4 in 80% ee. Decreasing the amount of the chiral Lewis acid catalyst led to a decrease of both the ee and the yield. Desilylation of the 2-oxazolidine 1 was effected in CHCl$_3$ using catalytic amounts of p-toluenesulfonic acid (PTSA). Though the yield of the in situ-generated 2-oxazolidine 2 bearing the 1,3-oxazolidin-2-one auxiliary was perfect, purification of 2 by silica gel chromatography was problematic due to decomposition. No pure product was isolated from crude 2 by chromatography on silica gel. Decomposition occurred to a compound similar to 2, in which the 3-substituent was CH$_3$OH [49]. To overcome this problem, the crude reaction mixture containing 2 and PTSA was concentrated before excess Et$_3$N was added followed by CH$_3$OH as the solvent. These operations removed the 1,3-oxazolidin-2-one auxiliary while preserving the THP group, and afforded the corresponding methyl ester 3 (Table 1), which was stable and could be subjected to silica gel chromatography. Compound 4 was used to determine the stereoselectivity of the cycloaddition step as well as for oxidation.

Oxidation of the 2-oxazolidine 4 with Jones’ reagent gave a complicated mixture, in which the desired carboxylic acid was not observed (Scheme 2). The stepwise oxidation of the free hydroxy to the carboxy group via intermediary aldehyde was then examined. Swern or pyridinium chlorochromate (PCC) oxidation of 4 also gave a complicated mixture without the desired aldehyde detected. These failed reactions indicated that the 2-oxazolidine moiety could not survive oxidation conditions. Based on this assumption, the corresponding silyl nitronate from 3-nitropropanal or its acetal were not tried for cycloaddition.

We then set to liberate the β-hydroxy ketone synthon by ring opening of the isoxazoline 3 (Scheme 3). Raney-Ni-catalyzed hydrogenolysis in the presence of boronic acid had been widely utilized to disconnect the N–O bond as well as to hydrolyze the resulting imine into a ketone [52]. We applied this method to deprotect the isoxazoline 3. However, the desired β-hydroxy ketone was never obtained. In one instance, the methyl ketone from a retro-aldol reaction of the desired β-hydroxy ketone was observed. In our experience, the hydrogenolysis of a 2-oxazolidine having a 5-ester group was troublesome. Thus, the 5-ester group was reduced with NaBH$_4$ to give 5. The hydroxy group was subsequently protected with benzoyl (Scheme 3), which also worked as a chromophore facilitating HPLC analysis. Afterwards, we tried oxidations once again. After removal of THP from 6, the resulting compound 6’ was subjected to oxidation with various reagents (Scheme 4) [53-55]. The expected carboxylic acid or aldehyde was not observed, which further verified the intolerance exemplified in Scheme 2. These results prompted us to try the oxidation in a later stage.

When 6 was subjected to Raney-Ni-catalyzed hydrogenolysis, the desired β-hydroxy ketone 7 was obtained in 85% yield (Scheme 3). Under the weakly acidic conditions, the THP group survived. Next, a Narasaka–Prasad reduction [4-11] of 7 using Et$_2$BOMe and NaBH$_4$ at −78 °C gave stable ethylboronate 8 in 96% yield. Several ethylboronate compounds have been reported [9-11,56-62]. From 8 to 9, no H$_2$O$_2$ treatment was necessary. Rotary evaporation of 8 with CH$_3$OH at ca. 40 °C easily removed the ethylborane group. Removal of THP in 9 delivered a 1,3,5-trihydroxy compound 10. In another way, 10 could be prepared by treating 8 with PTSA in CH$_3$OH at rt. NMR spectra of 8-10 exhibited only one set of signals corresponding to the syn-dihydroxy products, indicating an extra high diastereoselectivity (syn:anti >99:1) during the reduction. To unambiguously determine the diastereomeric ratio, the anti-1,3-diol corresponding to 10 was prepared from 7 by RuCl$_3$-PPh$_3$-catalyzed hydrogenation [63,64]. However, the two diastereomers had identical proton NMR spectra.

The terminal hydroxy group of 10 was protected with TBS [65-69] and the syn-hydroxy groups subjected to acetonization using PTSA and dimethoxypropane (DMP) to give 12 in 86% total yield [70]. Treatment of 12 with TBAF again liberated the terminal hydroxy group for further oxidation. RuCl$_3$-catalyzed
Scheme 3: Preparations of 16 and related syn-1,3-diol compounds.

Scheme 4: Attempted oxidations of 6'.
oxidation of 13 with NaIO₄ yielded the carboxylic acid 14 in 86% yield [70], which was reacted with Boc₂O to get the tert-butyl ester 15 [26,43,71]. The ee of 15 was determined as 74%. The racemic sample of 15 was prepared from racemic diethyl malate following known methods [26,27]. Finally, K₂CO₃-catalyzed methanolation gave 16 in 87% yield [26,27]. The absolute stereochemistry of 16 was confirmed by crystal structure analysis [72] and the specific rotation [28] of 17. Centimeter-long prismatic single crystals of 17 were obtained by slow evaporation of a petroleum solution.

Starting from 9, we tested several reactions in order to selectively protect the internal hydroxy groups (Scheme 5). Though not fruitful, these results deserve some comments. The PTSA-catalyzed acetonization of 9 using 2.0 equiv DMP gave the acetonide 18 in a quantitative yield. Treating 18 with a catalytic amount of PTSA in methanol gave 10, with the protecting groups removed except benzoyl. PTSA-catalyzed acetonization of 10 using 2.0 equiv DMP gave a mixture of two acetonides 19 and 13, which are separable by silica gel chromatography (Scheme 5a). In another trial (Scheme 5b), acylation of the two hydroxy groups in 9 yielded 20 in a quantitative yield. PTSA-catalyzed removal of THP in 20 in methanol did occur. However, concomitant monodeacylation as well as further an acyltransfer reaction also took place, resulting in a mixture. These results indicated THP, isopropylidene or Ac protection to primary or secondary hydroxy groups did not well tolerate PTSA-catalyzed methanolation.

Conclusion
In conclusion, we synthesized tert-butyl (3S,5R)-6-hydroxy-3,5-O-isopropylidene-3,5-dihydroxyhexanoate (16), which is enantiomeric to a key intermediate for atorvastatin, from a chiral 2-isoxazoline (3). The β-hydroxy ketone 7 obtained from 3 could be easily converted into several syn-1,3-diols analogs, demonstrating the usefulness of chiral 2-isoxazolines.

Experimental
1: To a dry Schlenk tube were added Cu(OTf)₂ (144 mg, 0.4 mmol), chiral bisoxazoline B (139 mg, 0.52 mmol) and anhydrous CH₂Cl₂ (4 mL) under N₂. After stirring at room temperature for 2 h, a clear solution had formed, which was cooled to −50 °C and N-acryloyl-1,3-oxazolidin-2-one (282 mg, 2 mmol) was added. After stirring for 30 min, a solution of the silyl nitronate (3.0 mmol) in anhydrous CH₂Cl₂ (6 mL) was added. The mixture was stirred for 8 h at −50 °C and monitored by TLC. After the reaction was completed, the product was purified by silica gel chromatography. Yellow oil (923 mg, 95% yield); Rf 0.40 (1:1 hexanes/AcOEt); ¹H NMR (400 MHz, CDCl₃) δ 5.77–5.74 (m, 1H, CH₂CΗ,O), 4.53 (s, 1H, OCHO),
4.44 (t, J = 8.0 Hz, 2H, CH₂O), 4.03–3.99 (m, 2H, CH₂O), 3.79–3.74 (m, 2H, OCH₂CH₂), 3.47–3.37 (m, 3H, NCH and NCH₂), 2.75–2.66 (m, 1H, CHCH₂CH), 2.31–2.27 (m, 1H, CHCH₂CH₂), 2.17–2.12 (m, 1H, CH₂CH₂), 1.84–1.79 (m, 2H, CH₂CH₂ and CH₂CH₂CH₂), 1.68–1.49 (m, 6H, CH₂CH₂CH₂), 1.24–1.15 (m, 3H, SiCH), 1.07–1.01 (m, 18H, SiCH(C₂H₅)₂), 1.0–1.05 (m, 1H, OC₂H₅), 3.68 (s, 3H, C₂H₅O), 3.88–3.82 (m, 1H, C₂H₅O), 4.92–4.87 (m, 1H, OC₂H₅), 4.51–4.50 (400 MHz, CDCl₃ δ 0.42 (1:1 hexanes/AcOEt); (0.41 g, 89% yield); (0.86 g, 1.78 mmol) in CHCl₃ (15 mL) was applied to remove the solvent before Et₂O was added PTSA (31 mg, 0.178 mmol) at 0 °C. The mixture was stirred overnight at room temperature. The crude mixture was purified by column chromatography. Yellow oil product was purified by column chromatography. Yellow oil was obtained from column chromatography. Total yield after purification was 0.41 g. The product was characterized by various spectroscopic techniques. The mass spectrum showed a peak at m/z 354 (M+H)⁺, indicating the molecular weight of the compound. The elemental analysis and mass spectral data matched the expected values.

3: To a solution of 1 (0.86 g, 1.78 mmol) in CHCl₃ (15 mL) was added PTSA (31 mg, 0.178 mmol) at 0 °C. The mixture was stirred overnight at room temperature. The crude product was purified by column chromatography. Yellow oil (0.41 g, 89% yield); Rf 0.42 (1:1 hexanes/AcOEt); 1H NMR (400 MHz, CDCl₃) δ 4.92–4.87 (m, 1H, OCH₂CO), 4.51–4.50 (m, 1H, OCHO), 3.88–3.82 (m, 1H, CH₂O), 3.75–3.71 (m, 1H, CH₂O), 3.68 (s, 3H, CH₃), 3.56–3.50 (m, 1H, CH₂O), 3.42–3.39 (m, 1H, CH₂O), 3.24–3.31 (m, 1H, CHCH₂CH), 2.62–2.54 (m, 1H, CH₂CH₂CH₂), 1.74–1.44 (m, 6H, CH₂CH₂CH₂), 1.35–1.3 (m, 3H, CH₃), 1.09–1.05 (m, 1H, CH₂CH₂CH₂), 1.0–1.05 (m, 1H, CH₂CH₂CH₂). 13C NMR (100 MHz, CDCl₃) δ 171.0, 156.9, 99.0, 98.9, 64.4, 64.3, 62.5, 62.4, 52.6, 41.6, 30.6, 27.9, 25.4, 19.6, 19.5; IR (cm⁻¹): 3481, 2950, 2873, 2852, 2657, 1756, 1738, 1734, 1628, 1456, 1436, 1367, 1354, 1211, 1344, 1030, 869, 814, 752, 740; ESIMS (m/z): [M + Na]⁺ calcd for C₁₅H₁₉NO₅S, 509.2659; found, 509.2659.

Supporting Information File 1
Experimental procedures and characterization data. [https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-15-179-S1.pdf]

Supporting Information File 2
Crystallographic data for 17. [https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-15-179-S2.cif]

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72. Crystallographic data of 17: CCDC 1826709.

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