Asymmetric Syntheses of (2*R*,3*S*)-3-Hydroxyproline and (2*S*,3*S*)-3-Hydroxyproline

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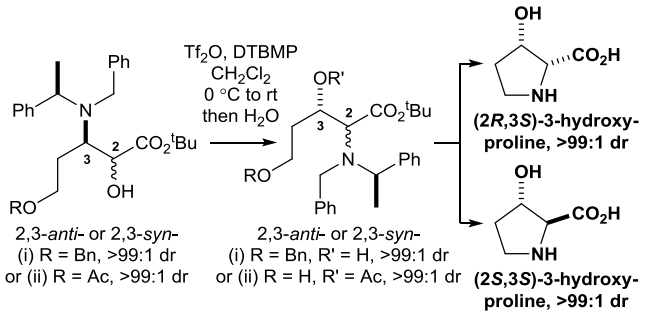
Supporting Information Placeholder



ABSTRACT: Two synthetic routes have been developed for the asymmetric syntheses of (2*R*,3*S*)- and (2*S*,3*S*)-3-hydroxyproline. The key synthetic step in each of these strategies is the conversion of protected α,δ-dihydroxy-β-amino esters (either 2,3-*anti*- or 2,3-*syn*-configured) into β,δ-dihydroxy-α-amino esters (protected forms thereof), via the intermediacy of the corresponding aziridinium ions. The products of these stereospecific rearrangements were then cyclized and deprotected to afford (2*R*,3*S*)-3-hydroxyproline and (2*S*,3*S*)-3-hydroxyproline as single diastereoisomers (>99:1 dr) in >26% overall yield.

(2*R*,3*S*)-3-Hydroxyproline **5** and its epimer (2*S*,3*S*)-3-hydroxyproline **6** (*cis*- and *trans*-3-hydroxyproline, respectively) have been isolated from a wide variety of natural sources, including a dried Mediterranean sponge,[1] hydrolysates of the antibiotic telomycin,[2] and collagen of varied origins,[1b,3] and have also been identified as constituents of other natural products.[4,5] Accordingly, these amino acids have inspired significant interest from synthetic chemists, with several enantiospecific[6] and asymmetric[7] syntheses being reported to date, in addition to enzymatic methods for their preparation.[8]

We have recently published several procedures concerning the utility of aziridinium intermediates derived from enantiopure α-hydroxy-β-amino esters,[9] and envisaged that this methodology could be used as a key step in syntheses of (2*R*,3*S*)- and (2*S*,3*S*)-3-hydroxyproline **5** and **6**. 2,3-*anti*-α-Hydroxy-β-amino esters **1** (bearing suitable functionality "X" at the δ-position) are readily accessible using our diastereoselective aminohydroxylation methodology.[10] Epimerization of **1** at the C(2)-position can then be achieved via an oxidation/diastereoselective reduction approach to give the corresponding 2,3-*syn*-epimers **2**.[9d] Activation of the C(2)-hydroxyl group within **2** would then give aziridinium species **3**, and regioselective ring-opening of **3** with H_2O would provide access to β-hydroxy-α-amino ester **4**. Subsequent cyclisation of **4** using the pendant functionality "X" as a synthetic handle would then give, after deprotection, (2*R*,3*S*)-3-hydroxyproline **5**. (2*S*,3*S*)-3-Hydroxyproline **6** would also be targeted via elaboration of 2,3-*anti*-**1** using a similar approach (Figure 1).

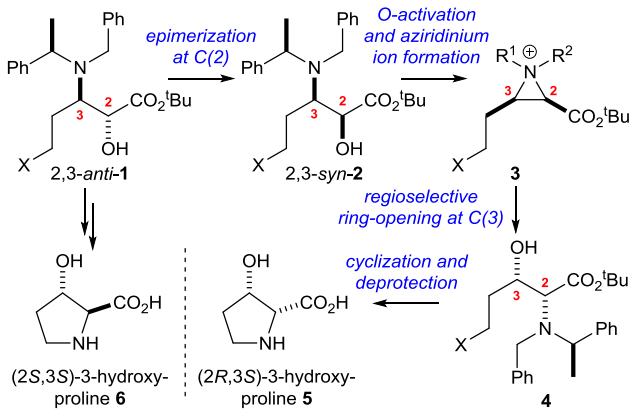
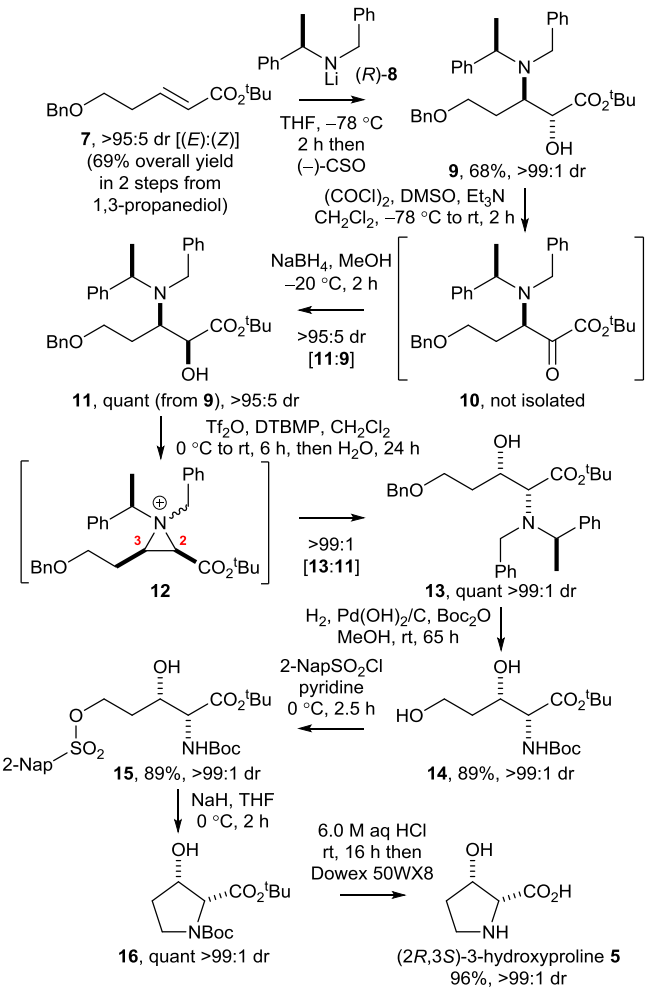


Figure 1. Proposed strategy towards 3-hydroxyprolines **5** and **6**.

Our initial strategy employed an *O*-benzyl protected hydroxyl group at the δ-position. The requisite α,β-unsaturated ester **7** was prepared from 1,3-propanediol upon mono-*O*-benzyl protection and one-pot Swern oxidation/Wittig reaction, which gave **7** ($^3J_{2,3}$ = 15.5 Hz) in 69% overall yield and >95:5 dr [(*E*):(*Z*)]. Diastereoselective aminohydroxylation[10] of **7** was achieved upon sequential treatment with enantiopure lithium amide (*R*)-**8** and (–)-camphorsulfonyloxaziridine [(–)-CSO], which gave 2,3-*anti*-α-hydroxy-β-amino ester **9** in 68% yield as a single diastereoisomer (>99:1 dr). The stereochemical outcome of this reaction was assigned by analogy to the well-established result of this aminohydroxylation protocol.[10] Oxidation of **9** under Swern conditions, followed by treatment

of the intermediate ketone **10** with $NaBH_4$ at –20 °C gave 2,3-*syn*-α-hydroxy-β-amino ester **11** in quantitative yield (from **9**) and >95:5 dr. Following our established procedure for interchanging the positions of the amino and hydroxyl substituents within α-hydroxy-β-amino esters,[9a] treatment of **11** with Tf_2O and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) gave β-hydroxy-α-amino ester **13** exclusively, and **13** was isolated in quantitative yield and >99:1 dr after purification. The configuration of **13** was initially assigned on the basis that this is a stereospecific rearrangement process proceeding via the intermediacy of the corresponding aziridinium species **12** [which involves sequential inversion of configuration at both C(2) and C(3)], and this assignment was subsequently confirmed upon elaboration to (2*R*,3*S*)-3-hydroxyproline **5**. Hydrogenolysis of **13** in the presence of Boc_2O gave **14** in 89% isolated yield, and regioselective sulfonylation of the primary hydroxyl group within **14** upon treatment with 2-naphthalenesulfonyl chloride (2-$NapSO_2Cl$)[6g] was followed by cyclisation to give pyrrolidine **16** upon treatment of the resultant sulfonate ester **15** with NaH; following purification of the crude reaction mixture, **16** was isolated in 89% yield (from **14**) and >99:1 dr. Hydrolysis of **16** finally liberated the target amino acid, and following purification via ion exchange chromatography on Dowex 50WX8 resin, (2*R*,3*S*)-3-hydroxyproline **5** was isolated in 96% yield and >99:1 dr (Scheme 1). The melting point, specific rotation and spectroscopic data for this sample of **5** were all in agreement with the literature values {mp 217–223 °C (dec.); lit.[6i] mp 210–217 °C (dec.); $[\alpha]_D^{25}$ +80.9 (*c* 1.0 in H_2O); lit.[6i] $[\alpha]_D^{20}$ +96.3 (*c* 0.92 in H_2O)}, thereby confirming the assigned configurations of all synthetic precursors. Overall, (2*R*,3*S*)-3-hydroxyproline **5** was produced in 35.7% yield in 9 steps from 1,3-propanediol.

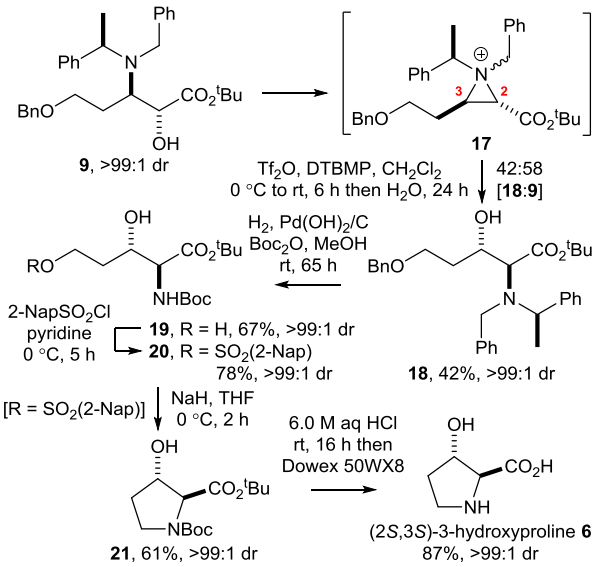
Scheme 1. Synthesis of (2*R*,3*S*)-3-Hydroxyproline 5



Identical treatment of *anti*-α-hydroxy-β-amino ester **9**, following our established procedure for interchanging the positions of the amino and hydroxyl substituents,[9a] gave a 42:58 mixture of β-hydroxy-α-amino ester **18** and α-hydroxy-β-amino ester **9**, respectively, from which **18** was isolated in 42% yield and >99:1 dr.[11] The configuration of **18** was initially assigned on the basis that this is a stereospecific rearrangement process proceeding via the intermediacy of the corresponding aziridinium species **17**, and this assignment was subsequently confirmed by single crystal X-ray diffraction analysis of a derivative. Upon repetition of this reaction using $H_2{}^{18}O$ as the nucleophile, the ^{18}O isotopic label was fully incorporated into the products ^{18}O-**18** and ^{18}O-**9** (as determined by mass spectrometric analysis) and therefore the presence of returned **9** cannot be attributed to unreacted starting material.[12] The stereospecific conversion of ^{16}O-**9** into ^{18}O-**9** is entirely consistent with the reaction proceeding via the intermediacy of aziridinium intermediate **17**, with unusually poor regioselectivity upon aziridinium ring-opening being observed. Although the regioselectivity is anomalously low here [indeed this is the only example that we have investigated to date where ring-opening is actually (albeit only marginally) favoured at the C(2)-position], we have previously observed that slightly inferior regioselectivity is observed for ring-opening of an aziridinium species derived from 2,3-*anti*-α-hydroxy-β-amino esters when compared to the corresponding reactions of

the epimeric 2,3-*syn* substrates, and that inductive effects are a significant factor in determining regioselectivity upon aziridinium ring-opening;[9d] presumably the combination of the *anti*-relative configuration and the inductively electron withdrawing influence of the benzyloxy substituent is responsible for the poor regioselectivity in this case. Subsequent elaboration of **18** upon hydrogenolysis in the presence of Boc_2O gave **19** in 67% isolated yield, and regioselective sulfonylation followed by cyclisation gave pyrrolidine **21** in 48% yield (from **19**) and >99:1 dr (Scheme 2).

Scheme 2. Initial Synthesis of (2*S*,3*S*)-3-Hydroxyproline 6



The relative configuration within **21** was unambiguously established via single crystal X-ray diffraction analysis of the solvate **21**·$CHCl_3$,[13] and the absolute (*S*,*S*)-configuration of **21** was determined upon refinement of a Flack *x* parameter[14] of –0.015(10) for the structure of **21**·$CHCl_3$, which satisfies the criteria for a reliable assignment of absolute configuration of a material known to be enantiopure (Figure 2). These data thereby also serve to confirm the absolute configurations within the synthetic precursors **9** and **18**–**20**. Hydrolysis of **21** finally liberated the target amino acid, and following purification via ion exchange chromatography on Dowex 50WX8 resin, (2*S*,3*S*)-3-hydroxyproline **6** was isolated in 87% yield and >99:1 dr (Scheme 2). The melting point, specific rotation and spectroscopic data for this sample of **6** were all in agreement with the literature values {mp 231 °C (dec.); lit.[6i] mp 231–234 °C (dec.); $[\alpha]_D^{25}$ –15.8 (*c* 1.0 in H_2O); lit.[6i] $[\alpha]_D^{20}$ –18.8 (*c* 0.92 in H_2O)} and the configuration of **6** was confirmed via single crystal X-ray diffraction analysis of the monohydrate **6**·H_2O for which a Flack *x* parameter[14] of –0.1(3) was determined, thus confirming the anticipated absolute configuration (Figure 2). Overall, (2*S*,3*S*)-3-hydroxyproline **6** was produced in 5.5% yield in 8 steps from 1,3-propanediol.

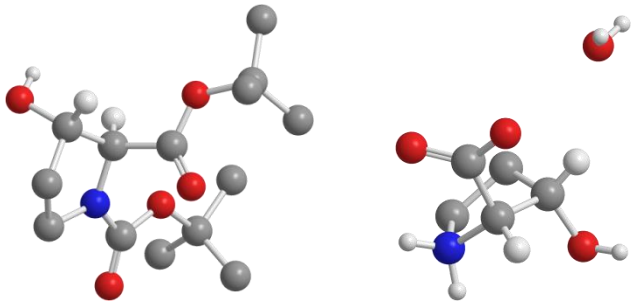
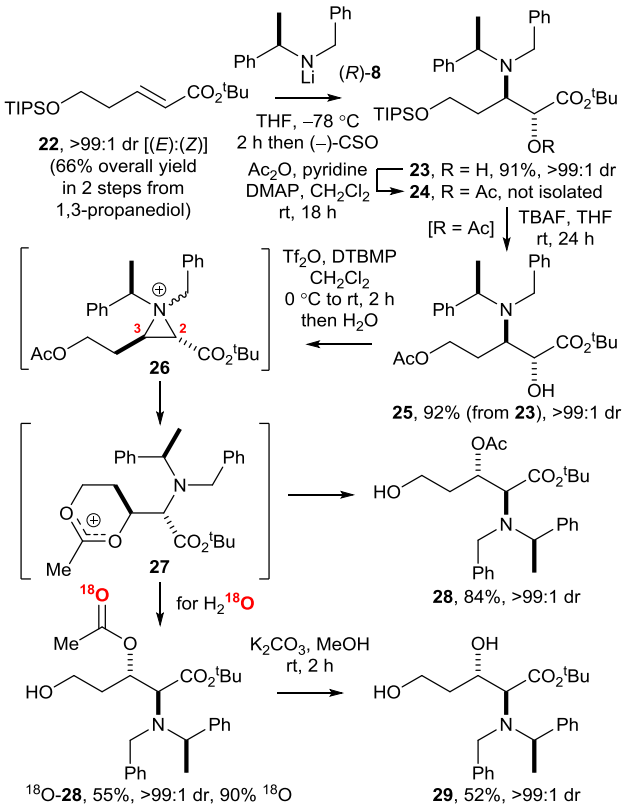


Figure 2. X-ray crystal structures of **21**·$CHCl_3$ [*left*] and (2*S*,3*S*)-3-hydroxyproline monohydrate **6**·H_2O [*right*] (selected H atoms and $CHCl_3$ have been omitted for clarity).

In order to address the issue of the relatively poor regioselectivity of aziridinium ring-opening in the *anti*-diastereoisomeric series, an alternative strategy was devised whereby a tethered nucleophile (i.e., an acetate group) would promote ring-opening at the C(3)-position. The requisite δ-acetoxy substituted α-hydroxy-β-amino ester **25** was also prepared from 1,3-propanediol: mono-*O*-silyl protection, followed by one-pot Swern oxidation/Wittig olefination gave α,β-unsaturated ester **22** ($^3J_{2,3}$ = 15.7 Hz; TIPS = triisopropylsilyl) in 66% overall yield and >99:1 dr [(*E*):(*Z*)]. Subsequent aminohydroxylation[10] of **22** gave 2,3-*anti*-α-hydroxy-β-amino ester **23** in 91% yield and >99:1 dr, and again the stereochemical outcome of this reaction was assigned by analogy to our well-established aminohydroxylation protocol.[10] Acetylation of the C(2)-hydroxyl group within **23**, followed by *O*-desilylation of **24** proceeded with concomitant acetyl migration to give δ-acetoxy substituted α-hydroxy-β-amino ester **25** in 92% yield (from **23**) and >99:1 dr (Scheme 3). The relative configurations of both **23** and **25** were unambiguously established via single crystal X-ray diffraction analyses (Figure 3),[13] and the absolute (*R*,*R*,*R*)-configurations within **23** and **25** were in each case assigned from the known (*R*)-configuration of the α-methylbenzyl fragment; these assignments were then confirmed upon refinement of Flack *x* parameters[14] of –0.01(2) and 0.00(11) for the structures of **23** and **25**, respectively. Treatment of **25** with Tf_2O and DTBMP gave β-acetoxy-δ-hydroxy-α-amino ester **28** in 84% yield and >99:1 dr. The formation of **28** as the sole product in this reaction is consistent with formation of the corresponding aziridinium ion **26** and intramolecular ring-opening of **26** at the C(3)-position by the tethered acetate group, followed by regioselective hydrolysis of the intermediate acetoxonium ion **27**. Upon repetition of this reaction using $H_2{}^{18}O$ for the hydrolysis of **27**, the ^{18}O isotopic label was fully incorporated into the product ^{18}O-**28** (as determined by mass spectrometric analysis), and subsequent cleavage of the *O*-acetyl group upon treatment of ^{18}O-**28** with K_2CO_3 and MeOH gave diol **29**, thereby confirming that the isotopic label was indeed located within the acetyl group and that the reaction outcome is therefore consistent with our mechanistic hypothesis (Scheme 3).[15] *O*-Tosylation of **28** followed by heating a solution of the resultant tosylate in MeCN promoted cyclisation and loss of the *N*-α-methylbenzyl group from the resultant pyrrolidinium intermediate[16] to give pyrrolidine **30** in 78% overall yield (Scheme 4). The relative configuration within **30** was unambiguously established via single crystal X-ray diffraction analysis (Figure 4),[13] and the absolute (*S*,*S*)-configuration of **30** was confirmed upon refinement of a Flack *x* parameter[14] of –0.03(15); this analysis therefore also confirmed the assigned configuration of **28**. Subsequent hy-

drogenolytic *N*-debenzylation and hydrolysis of both the *tert*-butyl ester and acetate groups gave (2*S*,3*S*)-3-hydroxyproline **6** {mp 230–234 °C (dec.); $[\alpha]_D^{25}$ –12.4 (*c* 1.0 in H_2O)} in 73% yield (from **30**) and >99:1 dr (Scheme 4). Overall, (2*S*,3*S*)-3-hydroxyproline **6** was produced in 26.4% yield in 9 steps from 1,3-propanediol via this route (i.e., an increase of 21% over our first generation synthesis). The application of this strategy in the synthesis of the epimeric target (2*R*,3*S*)-3-hydroxyproline **5** was also evaluated and gave **5** in 10 steps and 11.9% overall yield [full details can be found in the Supporting Information (SI)], although this approach was not superior to our in initial synthesis for which **5** was produced in 35.7% overall yield.

Scheme 3. Superior Regioselectivity via Aziridinium Ring-Opening with a Tethered Nucleophile



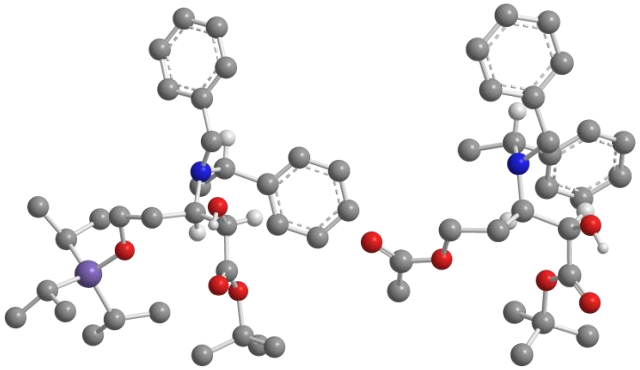
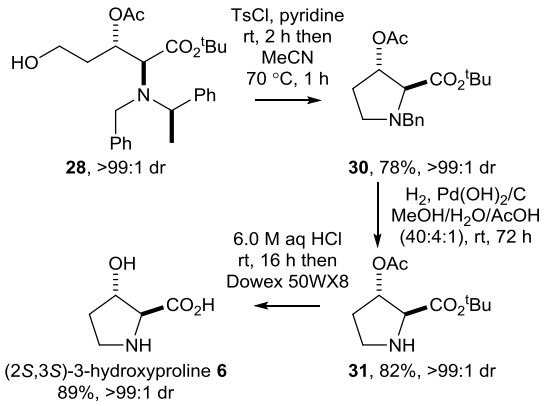


Figure 3. X-ray crystal structures of **23** [*left*] and **25** [*right*] (selected H atoms have been omitted for clarity).

Scheme 4. Elaboration to (2*S*,3*S*)-3-Hydroxyproline 6



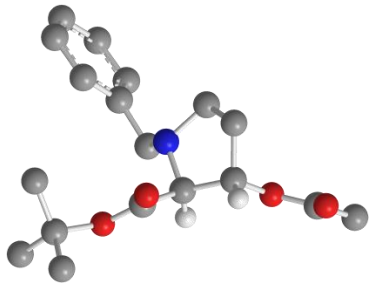


Figure 4. X-ray crystal structure of **30** (selected H atoms have been omitted for clarity).

In conclusion, the asymmetric syntheses of (2*R*,3*S*)-3-hydroxyproline and (2*S*,3*S*)-3-hydroxyproline were achieved via the diastereoselective aminohydroxylation of α,β-unsaturated esters, followed by conversion of the resultant enantiopure α-hydroxy-β-amino esters into the corresponding β-hydroxy-α-amino esters (or protected forms thereof). This stereospecific rearrangement process involves formation of the corresponding aziridinium species, upon activation of the C(2)-hydroxyl moiety, followed by aziridinium ring-opening with either H_2O or a tethered acetate group. These processes are applicable to both 2,3-*anti*- and 2,3-*syn*-α-hydroxy-β-amino esters and may be routinely performed on multigram scales. Following the optimal routes, subsequent cyclisation and deprotection gave (2*R*,3*S*)-3-hydroxyproline and (2*S*,3*S*)-3-hydroxyproline in 35.7 and 26.4% overall yield in 9 steps from commercially available 1,3-propanediol.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.xxxxx.
Experimental details, characterization data, and ^1H and ^{13}C NMR spectra (PDF)
X-ray diffraction data for structures CCDC 1846932–1846938 (CIF)

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Notes

The authors declare no competing financial interest.

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(11) α-Hydroxy-β-amino ester **9** was recovered in 55% yield and >99:1 dr, and was recycled in subsequent repetitions of this rearrangement process.

(12) In this case, ^{18}O-**18** (96% ^{18}O) and ^{18}O-**9** (96% ^{18}O) were isolated as single diastereoisomers (>99:1 dr) in 32 and 36% yield, respectively.

(13) Crystallographic data (excluding structure factors) for **5**, **6**·H_2O, **21**·$CHCl_3$, **23**, **25**, **30** and **39** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1846932–1846938, respectively.

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