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The Aldol-Tishchenko Reaction of Butanone, Cyclobutanone and a 3-Pentanone Derived Sulfinylimine and DFT Calculations of the Stereo-determining Step

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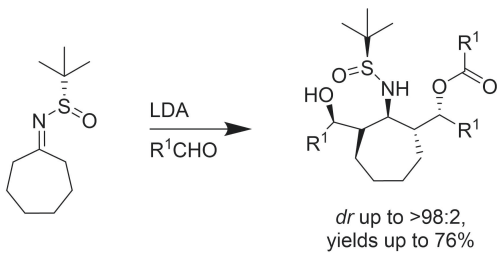
Abstract: Herein, we present a highly diastereoselective method to furnish acyclic 3-amino-1,5-diol derivatives using a tandem double-aldol-Tishchenko protocol (*dr* up to >99:1) using a butanone derived sulfinylimine. In most cases only 1 diastereomer predominates, from a possible 16. The reaction is also regioselective. In addition, the highly challenging cyclobutanone and 3-pentanone derivatives are also amenable to a double-aldol-Tishchenko reaction, although the *dr* values are modest. Despite that, clean single diastereomers can be isolated, which should prove very useful in medicinal chemistry and other areas. Detailed DFT calculations support the observed stereoselectivities in all cases, providing a rationale for the excellent *dr* values in the butanone series and the moderate values for the 3-pentanone class.

Introduction

1,3-Aminoalcohols, and derivatives thereof, form a key structural motif of many natural products and active pharmaceutical ingredients[1] (Figure 1). This class of compounds is also widely employed in asymmetric synthesis, and used extensively as chiral ligands and chiral auxiliaries (Figure 1).[2] Most of the current syntheses involve a two-step approach and the introduction of the chiral centres one at a time.[3] Early examples include the diastereoselective reduction of enantiomerically pure aldol products by Ellman[4,5] and other Mannich-type[6–9] products. A few examples of ring-opening reactions of chiral cyclic and bycyclic compounds[10] have also been reported in the literature, including pyranones,[11] piperidines[12–14] and tetrahydropyrans.[15] In recent years, transition metal-catalysed strategies have proven to be a successful approach for the construction of the 1,3-amino alcohol framework. High-profile examples include enantioselective C–H amination reactions,[16–18] allylic C–H amination reactions,[19–21] Pd-catalysed cyclisation reactions[22] and Rh and Ru-catalysed enantio- and diastereoselective hydrogenation reactions.[23,24] Although these methods represent highly sophisticated routes to the enantio- and diastereomerically enriched 1,3-amino alcohol framework, most still rely on the diastereoselective reduction of enantiopure compounds and thus introduce the chiral centres one at a time.

In fact, the introduction of multiple contiguous chiral centres, in this context, is quite rare.[25–27] Previous work from our group has described the aldol-Tishchenko reaction of chiral sulfinylimines as a method of accessing 1,3-amino alcohols (sometimes involving a number of contiguous chiral centres) and their derivatives, using simple and cheap starting materials in a one-pot procedure. Initially, a method to access highly enantio- and diastereomerically enriched 1,3-amino alcohols was reported through a single aldol-Tishchenko reaction of *N-tert*-butanesulfinylimines.[28–30] This was then further expanded to include a double aldol-Tishchenko reaction procedure, ultimately allowing access to highly enantio- and diastereomerically enriched 3-amino-1,5-diol derivatives (Scheme 1).[31]



Scheme 1. The double-aldol-Tishchenko reaction.

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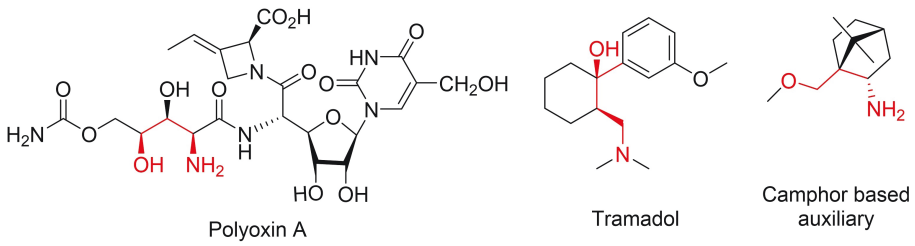
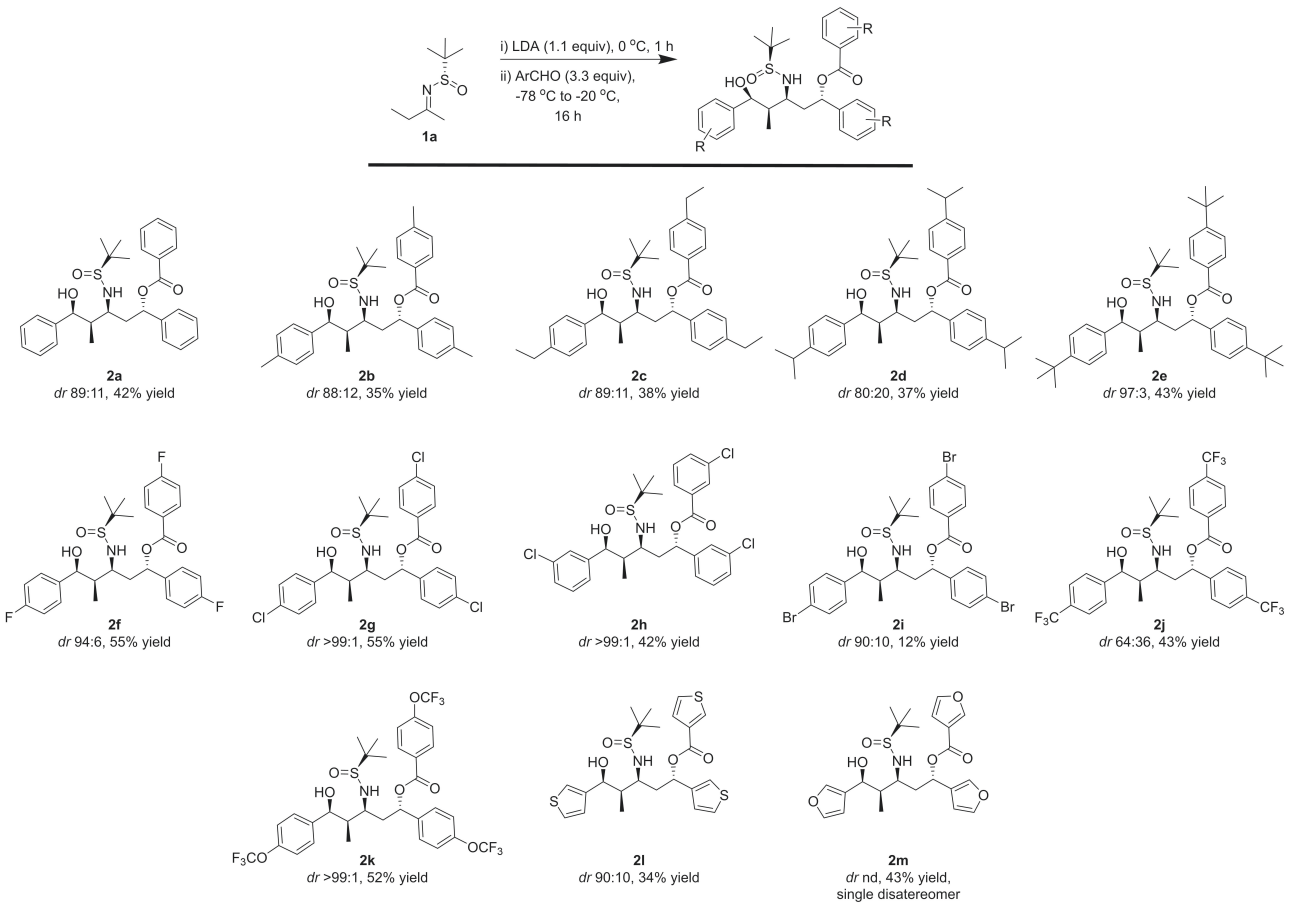


Figure 1. Examples of important 1,3-aminoalcohol containing compounds.

Herein, we describe further expansion of the double aldol-Tishchenko reaction of cyclic and acyclic chiral sulfinylimines, to include butanone, cyclobutanone and 3-pentanone derivatives. These highly functionalized compounds have great potential for synthetic utility, for example, as important medicinal scaffolds and effective chiral ligands, due to the number potential anchor-points present. We provide evidence (crystal structure) for the absolute stereochemistry of the 3-amino-1,5-diol derivatives synthesized. Detailed insight into the stereo-determining reaction step is provided by DFT calculations.

Results and Discussion

We initiated our double aldol-Tishchenko reactions using the butanone derived sulfinylimine **1a** (Scheme 2).[31] This challenging substrate possesses two possible sites for deprotonation: at the kinetically favoured methyl and the thermodynamically favoured methylene. Pleasingly, deprotonation of **1a** with LDA and subsequent reaction with benzaldehyde furnished **2a** in a regioselective manner. A moderate yield and good level of diastereoselectivity (42% yield, *dr* 89:11) was achieved with this substrate. The broad utility of the butanone framework[32,33] prompted us to investigate the scope of the reaction and investigate a range of aldol acceptors (**2b**–**2m**). Substitution at



Scheme 2. Substrate scope for the double-aldol-Tishchenko reaction using a butanone derivative.

the *p*-position of benzaldehyde (**2b**–**2e**) led to an increase in diastereoselectivity (*dr* up to 97:3). We next turned our attention to halogen-substituted benzaldehydes (**2f**–**2i**). With the exception of the brominated analogue (**2i**), excellent levels of diastereoselectivity were achieved for these substrates (up to >99:1). Excellent diastereoselectivity was also maintained when the position of the substituent was altered from *p*-chloro to *m*-chloro (**2g**, **2h**). Although a moderate yield was obtained, a substantial decrease in diastereoselectivity (*dr* 64:36) was observed when 4-trifluoromethylbenzaldehyde was employed as an aldol acceptor (**2j**). Once again, an excellent diastereoselectivity and moderate yield was observed when 4-(trifluoromethoxy) benzaldehyde was used as an aldol acceptor (**2k**). Excellent levels of diastereoselectivity and moderate yields were also observed when heteroaromatic aldehydes were employed (**2l**, **2m**). Some of the suspected side-products formed during this reaction that contribute to a reduced yield include double-aldol product, and reduction of the aldehyde to alcohol (perhaps as a result of the LDA reduction via a Meervein-Ponndorf-Verley-type hydride transfer).

Unfortunately, these substrates proved largely incompatible with crystallographic studies, with most failing to grow adequate quality crystals. However, degradation in toluene of one substrate did provide a single-crystal suitable for X-ray crystallographic analysis, allowing for determination of the absolute stereochemistry ((1*S*,2*R*,3*S*,5*S*) for **2a**) of this substrate (Figure 2).

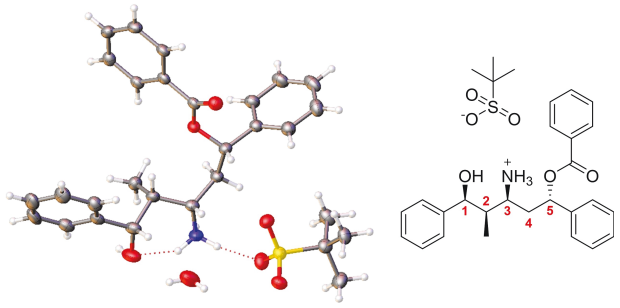
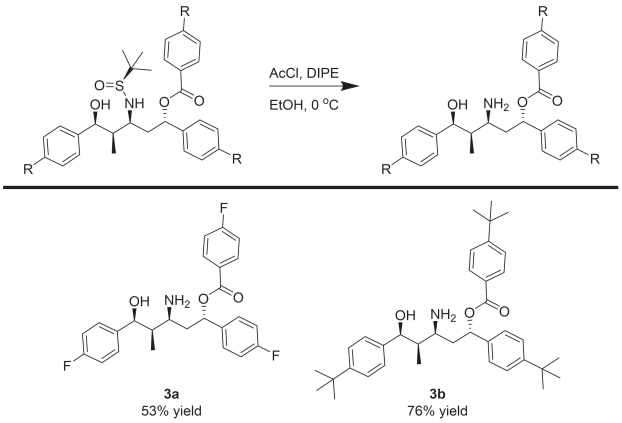


Figure 2. Crystal structure of the cleaved butanone derived double-aldol-Tishchenko product.



Scheme 3. Removal of the Ellman auxiliary.

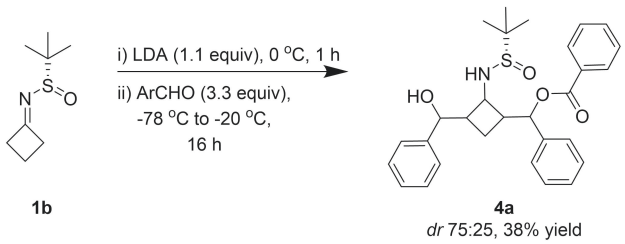
Removal of the chiral sulfinyl group could be achieved under mild reaction conditions (Scheme 3) in moderate to good yields, without any loss in diastereomeric purity to afford 3-amino-1,5-diol derivatives (**3a**, **3b**).

The cyclobutane moiety is often described as a prominent member of the medicinal chemist's toolbox due to several factors, including reduced issues associated with isomerisation when replacing alkenes, increasing conformational restriction and increased metabolic stability.[34] Drug candidates containing the cyclobutane moiety, such as antivirals,[35] anti-cancer agents[36] and autoimmune disease agents,[37] are the topic of extensive scientific research of late, and methods to furnish these highly functionalized cyclobutane derivatives are required. Methods to access 1,3-amino alcohol derivatives of cyclobutane are rare.[38–40] After our success with butanone derived substrates, we decided to focus our attention on expanding this methodology to include the cyclobutanone derived sulfinylimine **1b**. After a double-aldol-Tishchenko reaction, the corresponding 3-amino-1,5-diol derivative (**4a**) could be obtained in a moderate yield and diastereoselectivity (38% yield, *dr* 75:25) (Scheme 4). Although the diastereoselectivity for this reaction is moderate, it was possible to isolate both diastereomers in high purity.

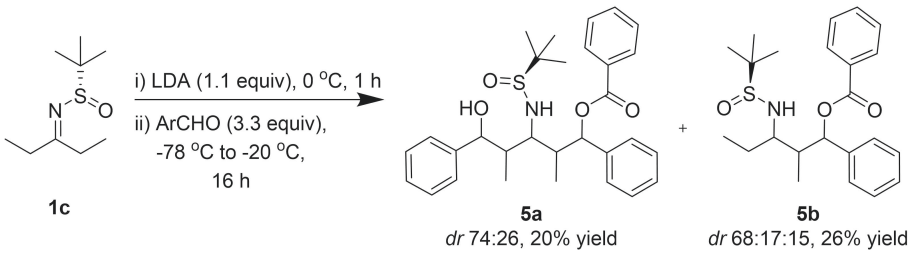
Finally, as pentanone represents a fundamental building block in organic and natural product synthesis,[41–43] we investigated the use of a symmetric, acyclic sulfinylimine, the 3-pentanone derivative **1c**. Here, a lower yield and diastereoselectivity (20% yield, *dr* 74:26) was obtained of the 3-amino-1,5-diol derivative (**5a**, Scheme 5). However, in this case it was again possible to obtain both diastereomers in high purity. It was also possible to isolate a single isomer of the aldol-Tishchenko product, 1,3-aminoalcohol derivative **5b**.

Density functional theory (DFT) calculations were then performed in order to analyse the origins of stereoselectivity in the double aldol-Tishchenko reactions of butanone and pentanone derived sulfinylimines, and to analyse the factors that lead to higher diastereoselectivity in one class of substrates compared to the other. Calculations were performed in Gaussian 16 using the B3LYP-D3/6-31G(d) level of theory for geometry optimizations and frequency calculations, and M06-2X/6-311+G(d,p) for single point energy calculations.

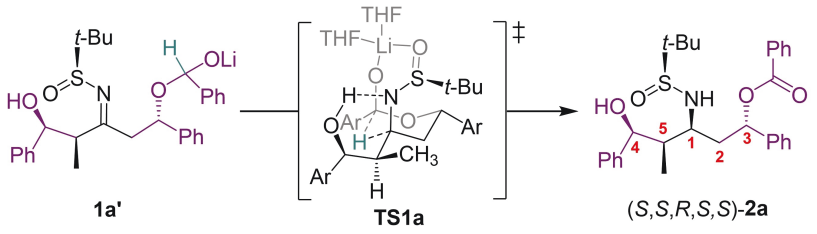
This reaction proceeds through two aldol reactions with two equivalents of aldehyde, followed by addition of another



Scheme 4. The double-aldol-Tishchenko reaction of a cyclobutanone derivative.



Scheme 5. The double-aldol-Tishchenko reaction of a pentanone derivative.



Scheme 6. The intramolecular hydride transfer step in the double-aldol-Tishchenko reaction of **1a**.

equivalent of aldehyde to form a hemiacetal (**1a'**, Scheme 6). This is followed by intramolecular hydride transfer through **TS1a** to form product **2a**. Our previous calculations of related reactions show that the stereodetermining step is the intramolecular hydride transfer to reduce the imine to the corresponding amine.[30,31] This one transition state (TS) controls the stereochemistry at each newly formed carbon centre, as all previous steps are reversible. Thus, we compared the relative TS barriers for intramolecular hydride transfer to form different diastereomers.

First, TSs were calculated for the reaction of butanone derived sulfinylimines to form **2a** and other unobserved possible diastereomers (Figure 3). Here, the six diastereomeric TSs that we expected to be lowest in energy were chosen. This decision was based on the lowest-energy TSs observed for the cycloheptanone derived substrates.[31] For the butanone derived substrate, the second-lowest energy TS led to the product with opposite stereochemistry at the hydroxy group. The difference between the two lowest-energy TSs (**TS1a** and **TS2a**) was 1.7 kcal/mol. This was the same energy difference as that observed in the cycloheptanone calculations for these two epimeric TSs.[6] In **TS1a**, a hydrogen bond interaction exists between the OH group at C4 and the nitrogen atom of the sulfinylimine, and the Ph group at C4 is *anti* with respect to the C1-C5 bond. In contrast, in **TS1b**, the analogous hydrogen bond leads to a distortion of this previously staggered system, with the Ph group at C4, as well as the OH at C4, being pushed towards the phenyl ring and THF group on the other side of the ring system. Similarly, the observed stereochemistry at C5, where the methyl group is in a pseudo-equatorial orientation, is favored because the opposite stereochemistry would place the methyl group in close proximity to the other side of the ring system, leading to unfavorable steric interactions (**TS1c**, see Supporting Information). Thus, the preferred relative stereochemistry between the substituents at C4, C5, and C1 will be *syn*. The stereochemistry at C3 allows for the Ph group to be in an equatorial orientation. The opposite stereochemistry at C3, where the Ph group is axial, leads to a 5.9 kcal/mol increase in energy (**TS1d**, see Supporting Information). Additional TSs are shown in the Supporting Information.

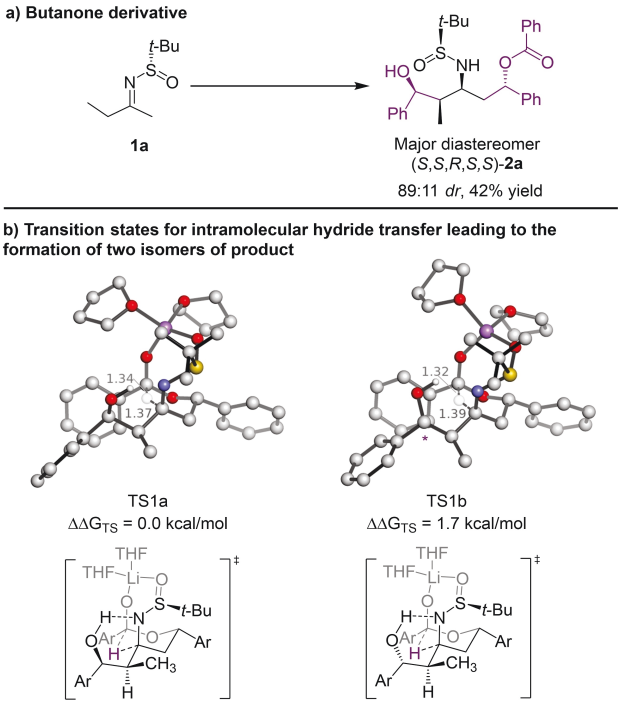


Figure 3. DFT calculations of the TSs leading to the formation of the major and minor diastereomers of **2a**.

Next, we calculated several hydride transfer transition states for the pentanone derived sulfinylimines (Figure 4 and Support-

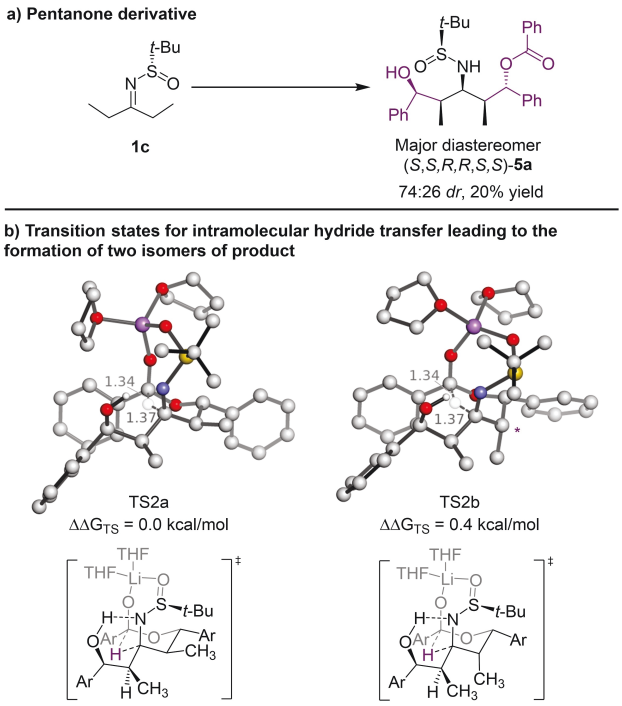


Figure 4. DFT calculations of TSs leading to the formation of the major and minor diastereomer of **5 a**.

ing Information). Experimentally, a lower diastereoselectivity was observed for these reactions (74 : 26 *dr*). This was consistent with the results of our calculations, which showed a small difference in energy between the two lowest energy TSs (**TS2a** and **TS2b**). These two diastereomers differ at the position of the methyl group on the chair during the transition state, which can be in an axial or equatorial orientation. At the M06-2X/6-311 + G(d,p)//B3LYP-D3/6-31G(d) level of theory, the axial orientation is 0.4 kcal/mol higher in energy than the equatorial orientation. This is in contrast to the previously calculated cycloheptanone derived system,[6] in which the axial orientation is 1.4 kcal/mol lower in energy, due to decreased steric interactions between the ring and the S-*t*-Bu, and decreased distortion of the cycloheptanone ring. However, using the functional and basis set that was used for the optimization and frequency calculations (B3LYP-D3/6-31G(d)), the opposite diastereomeric transition state is lower in energy, by 0.3 kcal/mol. The low preference for either TS is consistent with the low diastereoselectivity that is observed experimentally. We conclude that the major product observed experimentally is (*S,S,R,R,S,S*)-**5 a** or (*S,S,R,R,R,S*)-**5 a**, with other diastereomers proceeding through considerably higher energy transition state barriers (2.5 kcal/mol or greater). In this system, the stereochemistry at C1, C3, C4, and C5 is the same as the previously described stereochemistry of butanone derivative **2 a**, for the same reasons as described above. With the addition of another stereocenter at C2, there are now two TSs that are close in energy two each other, with these two TSs differing at the stereochemistry at C2. We thus conclude that in these systems, the relative stereochemistry of C1, C4, and C5 will be *syn*, and the stereochemistry at C3 will be *anti* to these groups; if the stereocenter at C2 is part of a ring system, it will be favorable to form the product with the relative *anti* stereochemistry at this position, but if it is not part of a ring system then the two epimers at C2 will arise from TSs that are close in energy, thus leading to a diminished diastereoselectivity.

In terms of the competing aldol, Tishchenko reaction to give **5 b**, we believe that the rate of the rate of the intramolecular hydride transfer competes with the rate of the second aldol reaction due to the low transition state barrier of the intramolecular hydride transfer, rather than a decreased rate of the aldol reaction. This is in contrast to the previously-studied cycloheptanone system, in which there is a significantly larger degree of steric hindrance between the cycloheptanone ring system and the other substituents in the 6-membered ring of the transition state. The transition state for intramolecular hydride transfer in the pentanone system does not experience such steric interactions due to the equatorial orientation of the substituents in this 6-membered ring transition state, thus leading to a lower transition state barrier that competes with the second aldol reaction.

Conclusion

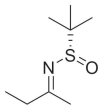
In summary, we have expanded our previously reported work to very useful moieties in medicinal and ligand chemistry. The more challenging substrates could, in the main, be used in an efficient one-pot process for the synthesis of acyclic 3-amino-1,5-diol derivatives, in good yields and good to excellent diastereoselectivities. This transformation has resulted in the introduction of 4 new stereogenic centres, where one stereoisomer predominates (out of a possible 16) and 3 new functionalities are introduced. The absolute stereochemistry of the major isomer has been elucidated by X-ray crystallography in one case, through a degradation product. Detailed mechanistic insights have been provided through DFT calculations.

Experimental Section

Representative experimental procedures/data are outlined below. All experimental procedures, characterisation data for all novel compounds, original spectra etc. are provided in the accompanying Supporting Information.

Synthesis and characterisation of (*S*)-*tert*-butyl sulfinimines: To a solution of titanium ethoxide (2 equiv.) in anhydrous THF (4 mL/mmol of ketone) was added ketone (1 equiv.) and (*S*)-*tert*-butanesulfinamide (1 equiv.). The resulting mixture was stirred at reflux and the reaction progress was monitored using TLC analysis. Upon completion of the reaction, the mixture was cooled to room temperature and brine (4 mL/mmol of ketone) was added. The resulting slurry was vigorously stirred for 30 min. This was then filtered through Celite®. The filtrate was washed with EtOAc and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure, affording the crude (*S*)-*tert*-butanesulfinylimine. Purification by column chromatography on silica gel gave pure (*S*)-*tert*-butanesulfinylimine.

(*S*)-*N*-(butan-2-ylidene)-2-methylpropane-2-sulfinamide, 1[a]

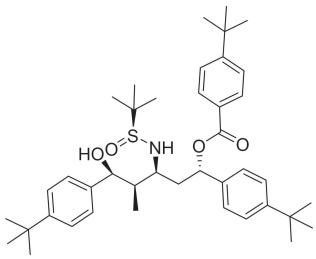


Prepared according to the general procedure outlined above using butanone (0.90 mL, 10 mmol) and (*S*)-*tert*-butanesulfinamide (1.21 g, 10 mmol). The crude product was purified by column chromatography on silica gel (4:1 hexane:EtOAc) to yield the title compound as a pale yellow oil (0.61 g, 35%).

Spectroscopic characteristics were consistent with previously reported data[31]

Synthesis of butanone derived 3-amino-1,5-diol precursors: To a Schlenk tube under N_2 atmosphere containing diisopropylamine (1.2 equiv.) and anhydrous THF (5 mL/mmol of sulfinylimine) was added *n*-BuLi (1.26 M in hexanes, 1.1 equiv.) dropwise at 0 °C. The resulting solution was stirred for 30 min before being cooled to −78 °C. Sulfinylimine (1 equiv.) was added dropwise and stirred for 1 h at this temperature. Freshly distilled aldehyde (3.3 equiv.) was added dropwise and the temperature was maintained at −78 °C for a further 3 h. The reaction mixture was warmed to −20 °C over 16 h. The reaction was quenched with NH_4Cl (2 mL) and allowed to warm to room temperature. The reaction was diluted with NH_4Cl (10 mL) and extracted with EtOAc (3×15 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography on silica gel yielded pure double aldol-Tishchenko product.

(1*S*,3*S*,4*R*,5*S*)-1,5-bis(4-(*tert*-butyl)phenyl)-3-(((*S*)-*tert*-butylsulfinyl)amino)-5-hydroxy-4-methylpentyl 4-(*tert*-butyl)benzoate



Prepared according to the general procedure outlined above using (*S*)-*N*-(butan-2-ylidene)-2-propane-2-sulfinamide (0.175 g, 1 mmol) and 4-*t*-butylbenzaldehyde (0.55 mL, 3.3 mmol). The crude compound (93:7 *dr*) was purified using column chromatography on silica gel (2:1, hexane:EtOAc) to give the title compound as a white solid (0.87 g, 43%).

Major diastereomer: M.p. 101–103 °C. $[\alpha]_D^{25} + 44.1$ (c 0.15, CH_2Cl_2). IR ν_{max} (ATR): 3259, 1632, 1137, 1076 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0. 90 (3H, d, $J = 7.1$ Hz), 1.29 (18H, s), 1.30 (9H, s), 1.35 (9H, s), 1.99–2.14 (2H, m), 2.15–2.27 (1H, m), 3.76–2.87 (1H, m), 4.09–4.32 (2H, m), 5.01 (1H, bs), 6.07 (1H, dd, $J = 10.1$, 3.4 Hz), 7.22–7.39 (10H, m), 7.46–7.49 (2H, m) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 6.3 (CH_3), 22.9 (3×CH_3), 31.1 (3×CH_3), 31.3 (3×CH_3), 31.4 (3×CH_3), 34.4 (qC), 34.6 (qC), 35.1 (qC), 42.9 (CH_2), 44.2 (CH), 56.4 (qC), 58.2 (CH), 73.0 (CH), 75.8 (CH), 125.0 (2×CH), 125.4 (2×CH), 125.5 (2×CH), 125.6 (2×CH), 126.0 (2×CH), 127.6 (qC), 129.5 (2×CH), 137.7 (qC), 141.0 (qC), 149.6 (qC), 150.9 (qC), 156.7 (qC), 165.7 (qC) ppm. HRMS (ESI) *m/z* calcd. for $C_{41}H_{60}NO_4S$ $[M+H]^+$: 662.4238, found 662.4252.

Deposition Number 2144096 (for **2a**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: 1,3-amino alcohol · DFT · diastereoselective · stereochemistry

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