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Highly diastereoselective allylation and reduction of chiral camphor-derived α-ketoamides

Neelesh A. Kulkarni, Shy-Guey Wang, Li-Chen Lee, Huei Ru Tsai, Uppala Venkatesham and Kwunmin Chen*

Department of Chemistry, National Taiwan Normal University, Taipei 116, Taiwan, ROC

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Abstract—The diastereoselective allylation and reduction of camphor-derived α-ketoamides to give optically enriched α-hydroxyl amides with high to excellent stereoselectivities are described. Allylation was carried out using allyltributylstannane in the presence of a stoichiometric amount of a Lewis acid to afford the desired homoallylic alcohols in relatively high chemical yields (up to 98%) and stereoselectivities (up to 98% de). Diastereoselective reductions were performed with the relatively bulky hydride K-Selectride at −78 °C to give the corresponding α-hydroxy amides in excellent chemical yields (up to 98%) and stereoselectivities (up to 98% de). The absolute configuration of the new stereogenic center of the major diastereomer was established by X-ray crystallographic analysis. Finally, stereochemical induction and the Lewis acid dependent reversal of stereoselectivity is described.

1. Introduction

The allylmetal addition and hydride reduction of a carbonyl functionality has been extensively studied for over the last few decades and has proven to be an enormously successful method for the construction of carbon–carbon bonds. The enantioselective version of allylation,[1] and hydride reduction,[2] of C=O and C=N functionalities, to produce the corresponding optically enriched alcohols and amines, have been documented in the literature. These utilities stimulated an important synergy between the fundamental studies of the stereochemistry and applications in target-oriented synthesis.[3] On the other hand, the diastereoselective allylation and reduction of an α-dicarbonyl functionality bearing a chiral auxiliary provide an alternative route to the preparation of important structural arrays.[4] The diastereoselective allylation of α-ketoamides to give homoallylic hydroxyl acid derivatives can be readily used in further functional group transformations.[5] The diastereoselective reduction of α-ketoamides, to produce chiral α-hydroxyl acid derivatives, which are fairly common structural units, that are useful in complex bioactive natural products synthesis, has been described.[6] Considerable interest has been focused on the development of novel methods for the preparation of two possible stereoisomers from a single chiral material, a topic that is at the forefront of synthetic organic chemistry.[7]

In continuation of our research interest in the area of asymmetric synthesis,[8] we herein report a full account of the diastereoselective allylation and hydride reduction of a variety of α-ketoamides, derived from camphor-based chiral auxiliaries (Xc = **A**–**C**) (Fig. 1) to give the corresponding α-hydroxy amides in high to excellent yields and diastereoselectivities. The stereochemical course of the reaction and proposed mechanisms for the reactions are discussed.

2. Results and discussion

The starting chiral α-ketoamides **1a**–**j** were readily prepared from the camphor-based chiral auxiliaries: camphor *N*-phenyl pyrazolidinone **A**, camphor *N*-tosyl-pyrazolidinone **B**,[9] and camphorsultam **C** and the chemical structures were unambiguously assigned by ^{1}H, ^{13}C NMR, HRMS as well as X-ray crystallographic analysis in some cases. A variety of aromatic, heteroaromatic and aliphatic α-ketoamides were utilized in the diastereoselective allylation and reduction reactions while the results are summarized in Tables 1–3.

* Corresponding author. Tel.: +886 2 89315831; fax: +886 2 29324249; e-mail: kchen@cc.ntnu.edu.tw

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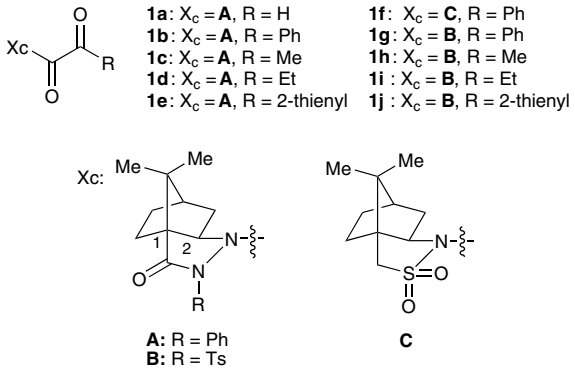
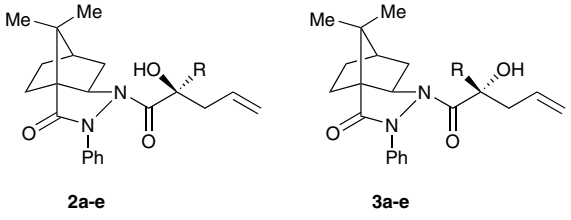


Figure 1. Structures of various camphor-derived α-ketoamides **1a**–**j**.

2.1. Asymmetric allylation

With various α-carbonyl amides in hand, we examined the diastereoselective allylation reaction. Treatment of camphor *N*-phenyl pyrazolidinone glyoxylate **1a**,[8a] with allyltributylstannane in the absence of a Lewis acid, provided the desired product in 50% yield and low stereoselectivity (Table 1, entry 1). Various Lewis acids, including $Sn(OTf)_2$, $Sc(OTf)_3$, $Sm(OTf)_3$ and $Yb(OTf)_3$, were then employed and all the reactions led to only modest stereoselection with good to high chemical yields (entries 2–5). The reactivity was improved upon when the reaction was carried out in the presence of $Eu(OTf)_3$ in CH_3CN (entry 6). The diastereoselectivity was determined by ^1H NMR analysis of the crude products as judged by the integration of the C-2 methine proton resonances (camphor numbering). The absolute configuration of the major diastereomer was assigned as an (*S*)-configuration based on a single crystal X-ray analysis. Solvent effects were then examined and CH_3CN found to be the solvent of choice for the reaction (entries 7–9). The use of 0.5 equiv of a Lewis acid provided the desired products in 91% yield, while the reaction proceeded sluggishly when 0.1 equiv of Lewis acid was used (entries 10 and 11). It thus appeared that the use of a stoichiometric amount of a Lewis acid in CH_3CN was

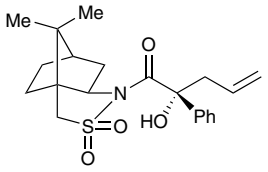
Table 1. Diastereoselective allylation of camphor *N*-phenylpyrazolidinone derived α-ketoamides **1a**–**e** with allyltributylstannane in the presence of a Lewis acid[a]



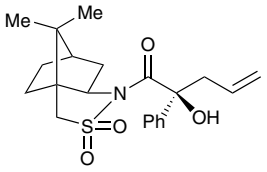
Entry	Substrate	Lewis acid (equiv)	Solvent	Time/h	Yield (%)[b]	Dr (**2**:**3**)[c]
1	**1a**	—	CH_3CN	168	50	55:45
2	**1a**	$Sn(OTf)_2$ (1.0)	CH_3CN	5 min	<20	—
3	**1a**	$Sc(OTf)_3$ (1.0)	CH_3CN	30 min	94	67:33
4	**1a**	$Sm(OTf)_3$ (1.0)	CH_3CN	20 min	88	70:30
5	**1a**	$Yb(OTf)_3$ (1.0)	CH_3CN	20 min	90	72:28
6	**1a**	$Eu(OTf)_3$ (1.0)	CH_3CN	5 min	90	75[d]:25
7	**1a**	$Eu(OTf)_3$ (1.0)	THF	5	75	43:57
8	**1a**	$Eu(OTf)_3$ (1.0)	CH_2Cl_2	30 min	85	42:58
9	**1a**	$Eu(OTf)_3$ (1.0)	Toluene	10 min	88	43:57
10	**1a**	$Eu(OTf)_3$ (0.5)	CH_3CN	10 min	91	71:29
11	**1a**	$Eu(OTf)_3$ (0.1)	CH_3CN	4	62	70:30
12	**1b**	$Eu(OTf)_3$ (1.0)	CH_3CN	72	50	72:28
13	**1b**	$Zn(OTf)_2$ (1.0)	CH_3CN	40 min	93	96:04
14	**1b**	$Sn(OTf)_2$ (1.0)	CH_3CN	5 min	95	99[d]:01
15	**1c**	$Sn(OTf)_2$ (1.0)	CH_3CN	5 min	89	77:23
16	**1c**	$Zn(OTf)_2$ (1.0)	CH_3CN	3	90	88:12
17	**1c**[e]	$Zn(OTf)_2$ (1.0)	CH_3CN	48	85	89:11
18	**1c**	$Eu(OTf)_2$ (1.0)	CH_3CN	72	51	26:74
19	**1d**	$Sn(OTf)_2$ (1.0)	CH_3CN	5 min	91	83:17
20	**1e**	$Sn(OTf)_2$ (1.0)	CH_3CN	5 min	92	99:01

[a] Unless otherwise noted, all reactions were carried out at ambient temperature using **1** (0.16 mmol), allyltributylstannane (2.0 equiv), a Lewis acid and the solvent indicated.
[b] Total isolated yield (**2** + **3**).
[c] Diastereomeric ratios was determined by ^1H NMR analysis of the relevant peaks and/or HPLC analysis [(Daicel chiralcel chiral OD column: 2-propanol/hexane = 05:95, 1.0 mL/min)] from the crude products.
[d] The absolute stereochemistry of the new stereogenic carbon center was determined by single crystal X-ray analysis.
[e] Reaction was performed at −30 °C.

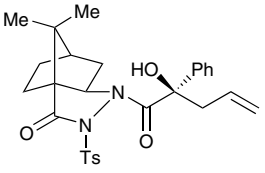
Table 2. Diastereoselective allylation of camphorsultam phenylglyoxylate **1f** and camphor *N*-tosylpyrazolidinone **1g** with allyltributylstannane in the presence of a Lewis acid[a]



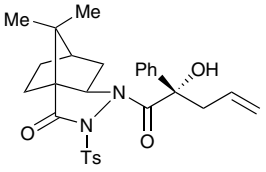
4f



5f



6g

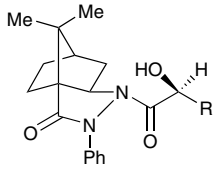


7g

Entry	Substrate	Lewis acid (equiv)	Solvent	Time/h	Yield (%)[b]	Dr (**4f**:**5f**)[c]	Dr (**6g**:**7g**)[c]
1	**1f**	$Sn(OTf)_2$ (2.0)	CH_3CN	48	62	87[d]:13	
2	**1f**	$Zn(OTf)_2$ (2.0)	CH_3CN	6	87	14:86	
3	**1f**	$ZnCl_2$ (2.0)	CH_3CN	72	92	14:86	
4	**1f**	ZnI_2 (2.0)	CH_3CN	72	95	12:88	
5	**1f**[e]	$Zn(OTf)_2$ (0.5)	CH_3CN	48	—	—	
6	**1f**	$Zn(OTf)_2$ (1.0)	CH_3CN	48	50	13:87	
7	**1f**	$Zn(OTf)_2$ (3.0)	CH_3CN	6	95	11:89[d]	
8	**1f**	$Zn(OTf)_2$ (3.0)	THF	24	95	11:89	
9	**1f**	$Zn(OTf)_2$ (3.0)	Toluene	24	95	55:45	
10	**1f**	$Zn(OTf)_2$ (3.0)	CH_2Cl_2	48	28	38:62	
11[f]	**1g**	$Sn(OTf)_2$ (2.0)	CH_3CN	5 min	92		99[d]:01
12[f]	**1g**	$PdCl_2$ (2.0)	CH_2Cl_2	24	60		06:94[d]

[a] Unless otherwise noted, all reactions were carried out at ambient temperature using **1** (0.16 mmol), allyltributylstannane (2.0 equiv), a Lewis acid and the solvent indicated.
[b] Total isolated yield.
[c] Diastereomeric ratios was determined by ^{1}H NMR analysis of the relevant peaks of the crude products.
[d] The absolute stereochemistry of the newly generated stereogenic center was determined by single crystal X-ray analyses of **4f**, **5f**, **6g** and **7g**.
[e] Trace amount of the products were observed.
[f] See Ref. 9.

Table 3. Diastereoselective reduction of camphor *N*-phenyl and *N*-tosylpyrazolidinone-derived α-ketoamides **1b–e** and **1g**, **i–j** with various reducing agents[a]



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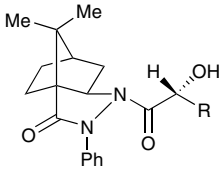

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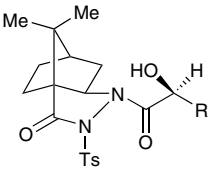

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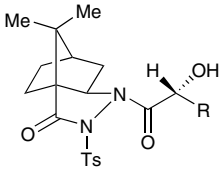

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b: R = Ph
c: R = Me
d: R = Et
e: R = 2-thienyl

g: R = Ph
i: R = Et
j: R = 2-thienyl

Entry	Substrate	Reductant	Solvent	Yield (%)[b]	Dr (**8**:**9**)[c]	Dr (**10**:**11**)[c]
1	**1b**	$NaBH_4$	MeOH	82	>99:01	
2	**1b**	$LiB(C_2H_5)_3H$	THF	90	>99:01	
3	**1b**[e]	K-Selectride	THF	50	>99:01	
4	**1b**	K-Selectride	THF	98	>99[d]:01	
5	**1c**	$NaBH_4$	MeOH	80	>99:01	
6	**1c**	$LiB(C_2H_5)_3H$	THF	92	>99:01	
7	**1c**	K-Selectride	THF	95	>99:01	
8	**1d**	K-Selectride	THF	96	>99[d]:01	
9	**1e**	K-Selectride	THF	98	>99[d]:01	
10[f]	**1g**	K-Selectride	THF	72		90:10[d]
11	**1g**	L-Selectride	THF	68		97:03
12	**1i**	L-Selectride	THF	65		97:03
13	**1j**	L-Selectride	THF	81		97:03

[a] Unless otherwise noted, all reactions were carried out at −78 °C using **1** (0.26 mmol), metal hydride (0.26 mmol) and the solvent indicated.
[b] Isolated yields of the products.
[c] Diastereomeric ratios was determined by ^{1}H NMR analysis of relevant peaks of the crude products.
[d] Absolute configuration of the newly generated stereogenic center was deduced from the X-ray crystallographic analysis **8b**, **8d–e** and **11g**.
[e] Reaction was performed at 0 °C.
[f] For entries 10–13, reactions were carried out at −78 °C using (0.43 mmol), metal hydride (0.86 mmol) in THF.

optimal for the reaction (entry 6). We next investigated the allylation of camphor *N*-phenyl pyrazolidinone phenylglyoxylate **1b**, under the developed conditions. Treatment of α-ketoamide **1b** under the same reaction conditions gave the product in 50% yield and 44% de (entry 12). Both the reactivity and stereoselectivity were improved when $Eu(OTf)_3$ was replaced with $Zn(OTf)_2$ under similar conditions (entry 13). Interestingly, this was further improved upon when $Sn(OTf)_2$ was used (entry 14). We then studied the substrate scope of the allylation reaction under optimum conditions. To this end, a high material yield and reasonable stereoselectivity were observed when camphor *N*-phenylpyrazolidinone methylglyoxylate **1c** was used (entry 15). However, the selectivity was improved to 76% de when $Zn(OTf)_2$ was employed instead of $Sn(OTf)_2$ (entry 16). It is noteworthy that the stereoselectivity was reversed when the reaction was carried out using several different Lewis acids (compare entries 16 and 18). The allylation reactions of aliphatic and hetero aromatic backbone architectures **1d–e** proceeded smoothly to give the corresponding allylation products in good to excellent stereoselectivities (entries 19 and 20).

The stereochemical outcome can be rationalized by invoking the conformational preferences of α-ketoamides **1b–e** in the transition state (Fig. 2).[10] The pseudo-planar *s-trans* conformation (A) of the α-dicarbonyl group in **1a–e** is electronically favored over its *s-cis* conformer (A′) in the solid state; this is supported by single crystal X-ray analyses of **1b–e**. This is due to the avoidance of dipole–dipole repulsions of the two carbonyl functionalities. However, the coordination of the Lewis acid metal ion to the dicarbonyl oxygen atoms shifted the reaction toward the formation of the *s-cis* conformation. The equilibrium between the different conformational states is highly dependent upon the type and amount of Lewis acid used in the reaction. From the data, we proposed that for strong Lewis acids, such as $Zn(OTf)_3$ and $Sn(OTf)_2$, the metal coordinates to the dicarbonyl oxygen atoms to give the desired major diastereomer. On the other hand, $Eu(OTf)_3$ coordinates to dicarbonyl oxygen atoms in most substrates while mono-coordinates to an oxygen atom in a specific substrate (**1c**). Spectroscopic evidence for the dual coordination behavior of $Sn(OTf)_2$ was obtained by ^{13}C NMR spectroscopy using camphor *N*-phenylpyrazolidinone phenylglyoxylate **1b**. The 100 MHz ^{13}C NMR spectrum of a mixture of $Sn(OTf)_2$ and **1b** (1:1) complex in CD_3CN at room temperature showed that the original dicarbonyl

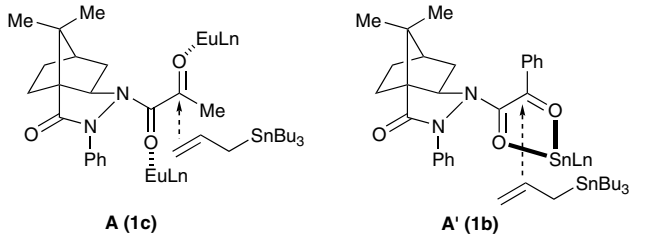

Figure 2. Proposed mechanism for the reaction of α-ketoamide **1b** and **1c** with allyltributylstannane in the presence of a Lewis acid.

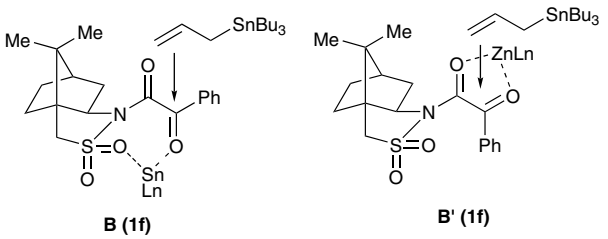

Figure 3. Proposed mechanism for the reaction of camphorsultam phenyl glyoxylate **1f** with allyltributylstannane in the presence of a Lewis acid.

signals at δ 160.60 and 189.40 ppm were shifted upfield to δ 160.47 and 189.22 ppm, respectively.[11] These results indicate that the Sn is strongly coordinated to dicarbonyl oxygen atoms, resulting in the formation of the preferred *s-cis* conformation. The major diastereoisomer is then obtained when the allyl reagent approaches from the less hindered bottom *si* face of the α-carbonyl group, to afford the desired product.

We further investigated the scope of the chiral auxiliaries; these results are presented in Table 2. Camphorsultam, one of the most widely used chiral auxiliaries, has great versatility in organic synthesis. Treatment of phenylglyoxylate **1f** with allyltributystannane using $Sn(OTf)_2$ afforded the desired product in good stereoselectivity (Table 2, entry 1). The absolute stereochemistry of the major diastereomer was assigned as an (*R*)-configuration by X-ray crystallographic analysis. It is interesting to note that a reversal of stereoselectivity occurred when $Zn(OTf)_2$ was used in place of $Sn(OTf)_2$ (entry 2). The influence of the Lewis acid in causing a reversal in stereoselectivity deserves special attention. The use of different Zn metals failed to improve the stereoselectivities (entries 3 and 4). The effects of the amount of Lewis acid was then studied. It is interesting to note that for camphor *N*-tosylpyrazolidinone **B** and camphorsultam **C** derived substrates, the use of more than 1.0 equiv of a Lewis acid was required to achieve high material yields (Table 2, entries 5–7). The use of 3.0 equiv of $Zn(OTf)_2$ provided **5f** in high chemical yield and stereoselectivity (entry 7). This may be due to the presence of the sulfone functionality in the auxiliaries **B** and **C**. Studies of solvent effects indicate that CH_3CN is the most effective solvent, affording the allylation product in 95% yield (entries 7–10).

We next investigated the allylation of camphor *N*-tosylpyrazolidinone phenylglyoxylate **1g** derived from chiral auxiliary **B**.[9] No reaction products were obtained when **1g** was treated with allyltributylstannane in the absence of a Lewis acid. Various metal triflates, including $Sc(OTf)_3$, $Sm(OTf)_3$, $Zn(OTf)_2$ and $Eu(OTf)_3$, were systematically screened, but resulted in either low to moderate chemical yields or low levels of diastereoselectivities (data not shown). Excellent stereoselectivity was obtained when the reaction was carried out in the presence of $Sn(OTf)_2$ in a 5 min reaction (entry 11).[9] The diastereoselectivity was determined from the ^1H NMR spectra of relevant peaks and an HPLC analysis of crude products.

The absolute stereochemistry of the new stereogenic center in the major diastereomer **6g** was assigned as an (*R*)-configuration, by means of X-ray crystallographic analysis. The reactivity decreased when the reaction was carried out in the presence of $PdCl_2$ with the major product with the reversed stereochemistry (entry 12). The structure of the major diastereomer **7g** was again confirmed by X-ray crystallographic analysis. A careful study of ^1H NMR spectra indicates that the characteristic C-2 methine proton (camphor numbering) appears at an upfield position (3.16 ppm) for the (*R*)-isomer compared with that of the counter (*S*)-product (4.32 ppm). The diamagnetic anisotropy effect of the aromatic substituent may account for the shielding effect.

The reversal of stereoselectivity in the allylation of **1f** and **1g** can be rationalized by the coordination of a Lewis acid with different Lewis base atoms, as shown in Figure 3. The results obtained for the allylation reaction of **1f** catalyzed by $Sn(OTf)_2$ can be explained by the formation of the chelated conformer **B**,[12] which is supported by IR spectroscopic data. Upon the addition of 1 equiv of the Lewis acid $Sn(OTf)_2$, the sulfonyl stretching band was shifted from 1042 to 1028 cm^{-1}. On the other hand, the sulfonyl group absorbs at 1038 cm^{-1} when complexed with 1 equiv of $Zn(OTf)_2$. The use of $Zn(OTf)_2$ afforded the desired products, which can be explained by the predominance of the chelated conformer **B′**, leading to the formation of the desired product. Additionally, the reversal of stereoselectivity in the allylation of **1g** was deduced from ^{13}C NMR and FTIR data.[9] The coordination of the $Sn(OTf)_2$ to the sulfonyl group resulted in the rapid release of the nucleophilic allyl group, which may account for the much faster reaction in the presence of $Sn(OTf)_2$ compared to the use of $PdCl_2$ (5 min vs 24 h). The allyl group then attacks the α-carbonyl group from the bottom *si* face to afford the desired product. In the case of $PdCl_2$, the electron-rich tosyl group prevents nucleophilic addition from the *si* face, leading to the addition from the top *re* face.

2.2. Asymmetric reduction

In the second aspect of the study, the diastereoselective reduction of the α-ketoamides was carried out and the results of these experiments tabulated in Table 3. Various chiral α-ketoamides were subjected to the reduction conditions and camphor *N*-phenylpyrazolidinone phenylglyoxylate **1b** was used as a model substrate. Treatment of **1b** with $NaBH_4$ in THF at 0 °C resulted in cleavage of the chiral auxiliary. Only a trace amount of the desired products were obtained when the reaction was carried out at −78 °C. A significant improvement in the chemical yield (82%) and excellent diastereoselectivity (>95% de) was achieved when a protic solvent, such as MeOH, was used at a lower temperature (entry 1). The material yield was slightly improved when a sterically demanding reducing reagent, such as $LiB(C_2H_5)_3H$, was employed (entry 2). The chemical yield decreased to 50% when K-Selectride was employed at 0 °C, but was improved significantly when the same reaction was carried out at −78 °C (entries 3 and 4). The absolute stereochemistry of the newly generated stereogenic center was assigned as an (*S*)-configuration by an X-ray crystallographic analysis of **8b**.

Substrate generality was then investigated for a wide variety of α-ketoamides **1b–e** under the optimized conditions. The reduction of the aliphatic ketone **1c** with $NaBH_4$ in MeOH provided the product in 80% material yield, while the use of $LiB(C_2H_5)_3H$ and K-Selectride resulted in excellent stereoselectivities (entries 5–7). The reduction of **1d** and a 2-thienyl substituent substrate **1e** was examined and excellent material yields and stereoselectivities were obtained (entries 8 and 9). Finally, the reduction of camphor *N*-phenylpyrazolidinone 3-indoloylglyoxylate with either $NaBH_4$ or K-Selectride virtually failed to yield any detectable products. This was presumably due to the presence of a ketone functionality in conjugation with the nitrogen of an indole, which could result in a decrease in the electrophilicity of the carbonyl carbon, thus leading to a lower reactivity.

Structural aspects of the chiral auxiliary were also investigated under the developed reaction conditions with the camphor *N*-tosylpyrazolidinone derived α-ketoamides **1g–j** (Table 3). Treatment of camphor *N*-tosylpyrazolidinone phenylglyoxylate **1g** in THF with K-Selectride at −78 °C gave the desired product in 72% chemical yield and good stereoselectivity (80% de) (entry 10). The diastereoselectivity was further improved to 94% when $LiB(C_2H_5)_3H$ was used (entry 11). The diastereomeric excess was determined by ^1H NMR analysis of the relevant peaks of the crude products. The absolute configuration of the newly generated stereogenic center in the minor diastereomer **11g** was determined to have an (*R*)-configuration, as deduced from a single X-ray crystal analysis. In the case of the methylglyoxylate derivative **1h**, cleavage of the auxiliary was observed under the conditions used for the reduction. High stereoselectivities were achieved in the case of the ethyl and thienyl derivatives **1i–j** (entries 12 and 13).

The stereochemical outcome of the asymmetric reduction may be rationalized by the conformational preference of pyrazolidinone derived α-ketoamides. The pseudo-planar *s-trans* conformation of the α-dicarbonyl group in **1b–e** is electronically favored over its *s-cis* conformer in the solid state as evidenced by X-ray crystallographic analyses (Fig. 4). This is due to the avoidance of dipole repulsion between the two carbonyl functionalities. In the *s-cis* conformation, the carbonyls (amide and carbonyl functionalities) are in close proximity, which causes mutual electronic repulsions. To avoid

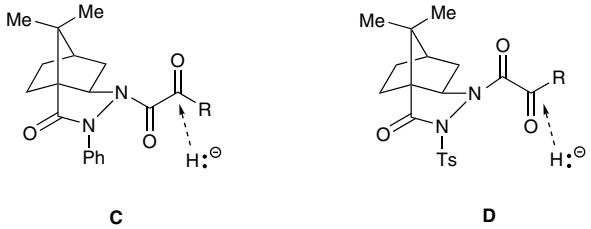

Figure 4. Proposed mechanism for the asymmetric reduction of α-ketoamides **1b–e** (Xc = A) and **1g**, **i–j** (Xc = B).

such repulsions at low temperatures, the carbonyls are oriented *anti* to each other. The carbonyl group of the amide is directed toward the phenyl ring of the pyrazolidinone moiety in **1b**–**e**, while they are directed away from the *N*-tosyl group in **1g**–**j**. For the allylation, the presence of a Lewis acid metal chelated to the dicarbonyl oxygen atoms, results in the formation of the preferred *s-cis* conformation. However, in the hydride reduction reaction the metal cation predominantly monocoordinates to the carbonyl moiety with an *s-trans* conformation. The bulkier camphor moiety shields the top face of the carbonyl group, thus permitting the hydride to attack from the sterically less hindered *re* face for **1b**–**d** (*si* face for **1e**). In the case of the camphor *N*-tosylpyrazolidinone derived α-dicarbonyl, the hydride attacks from the less hindered *re* face for **1g**–**i** and the *si* face for **1j**. This leads to the formation of the desired α-hydroxyl amides with a high level of stereoselectivity.

3. Conclusions

The diastereoselective allylation and reduction reactions of α-ketoamides derived from camphor-based chiral auxiliaries are operationally simple and the products can be obtained at synthetically useful level of chemical yields (up to 98%) and stereoselectivities (up to 98% de). The reversal of stereoselectivity was observed when different Lewis acids were used for the asymmetric allylation. For the asymmetric reduction of chiral α-ketoamides, high to excellent diastereoselectivities were generally obtained when a bulky hydride was used. The stereochemical outcome can be explained based on conformational preferences under the reaction conditions employed.

4. Experimental methods

4.1. General methods

All reagents were used as purchased from commercial suppliers without further purification. NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer (400 MHz for ^{1}H, and 100 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to an internal TMS standard for ^{1}H NMR and chloroform-*d* (δ 77.0) for ^{13}C NMR. Optical rotations were measured on a JASCO P-1010 polarimeter. EI mass spectra were recorded on Finnigan TSQ-700 at an ionizing energy of 70 eV and HRMS spectra were recorded on JEOL SX-102A. Routine monitoring of reactions was performed using silica gel, glass-backed TLC plates (Merck Kieselgel 60 F254) and visualized by UV light (254 nm). Solutions were evaporated to dryness under reduced pressure on a rotary evaporator and the residues purified by flash column chromatography on silica gel (230–400 mesh) with the indicated eluents. Air and/or moisture sensitive reactions were performed under the usual inert atmosphere conditions.

Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Center and allocated a CCDC deposit number.[13]

4.2. Procedure for the synthesis of (10,10-dimethyl-2-oxo-3-phenyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-oxo-acetaldehyde, 1a

Oxalyl chloride (3.3 mL, 34.7 mmol) was dissolved in CH_2Cl_2 (10 mL) and added slowly to *N*-phenyl camphorpyrazolidinone **1** (1 g, 3.9 mmol) in CH_2Cl_2 (5 mL) at ambient temperature. The mixture was stirred for 10 min and the solution concentrated in vacuo. The resulting crude product was dissolved in benzene (10 mL) and tributyl tinhydride (1.04 mL, 3.9 mmol) then slowly added. The reaction mixture was allowed to stir for 10 min at ambient temperature and quenched with H_2O (100 mL), extracted with EtOAc (3×75 mL). The layers were separated and the combined organic extracts dried over anhydrous $MgSO_4$ and concentrated. The resulting crude product was further purified by silica gel flash column chromatography eluted with hexane/EtOAc (2:1), to afford the pure product **1a** (0.99 g; 82%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (1H, s), 7.39–7.35 (2H, m), 7.24–7.22 (m, 3H), 4.54 (t, 1H, $J = 5.3$ Hz), 2.33–2.0 (m, 5H), 1.53–1.47 (m, 1H), 1.44–1.36 (m, 1H), 1.17 (s, 3H), 1.15 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 186.2, 170.0, 156.8, 128.7, 126.6, 123.4, 122.2, 68.9, 59.1, 52.4, 46.9, 40.4, 28.3, 26.5, 20.4, 19.9; HRMS (EI) calcd for $C_{18}H_{20}N_2O_3$ 312.1474. Found 312.1478.

4.3. Procedure for the synthesis of 1-(10,10-dimethyl-2-oxo-3-phenyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-phenyl-ethane-1,2-dione, 1b

Under a N_2 atmosphere, a mixture of phenylglyoxylic acid (0.64 g, 4.29 mmol) and thionyl chloride (10 mL, 137 mmol) was refluxed for 2 h at 75 °C and concentrated. The resulting crude product was dissolved in CH_2Cl_2 (5 mL). *N*-phenyl camphorpyrazolidinone **1** (1.0 g, 3.9 mmol) in CH_2Cl_2 (5 mL) was added, followed by stirring for 10 min at ambient temperature. The reaction mixture was quenched with H_2O (50 mL) and extracted with CH_2Cl_2 (3×50 mL). The layers were separated and the combined organic layers were dried over anhydrous $MgSO_4$. The resulting crude product was further purified by silica gel flash column chromatography eluted with hexane/EtOAc (2:1) to give the pure product **1b** (1.28 g; 85%): $[\alpha]_D^{27} = -144.8$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, 2H, $J = 8.1$ Hz), 7.61–7.56 (m, 1H), 7.47–7.42 (m, 3H), 7.38–7.36 (m, 3H), 7.20 (br s, 1H), 4.51 (t, 1H, $J = 4.9$ Hz), 2.28 (td, 1H, $J = 12.0$, 5.1 Hz), 2.06–1.86 (m, 4H), 1.52–1.47 (m, 1H), 1.32–1.29 (m, 1H), 1.26 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5, 170.2, 158.7, 136.9, 134.8, 132.9, 130.3, 128.8, 128.5, 126.4, 121.9, 68.3, 59.1, 52.2, 47.0, 39.0, 28.3, 26.4, 20.4, 19.8; HRMS (EI) calcd for $C_{24}H_{24}N_2O_3$ 388.1787. Found 388.1788; IR (neat, cm^{-1}): 3008, 2958, 2879, 1730, 1655, 1594, 1491, 1451, 1340, 1298, 1214, 1133, 962, 755; Crystal data for **1b** (colorless crystals, recrystallized from hexanes/EtOAc) at 25 °C: $C_{24}H_{24}N_2O_3$, $M = 388.467$, orthorhombic, $P2_12_12_1$,

$a = 10.1466$ (3) Å, $b = 10.9048$ (3) Å, $c = 18.8303$ (7) Å, $V = 2083.51$ (11) Å^3, $Z = 4$, $D_c = 1.238$ Mg/m^3, $\mu = 0.082$ mm^{-1}, 9170 reflections, 8137 parameters, $R = 0.052$, $Rw = 0.1267$.

4.3.1. 1-(10,10-Dimethyl-2-oxo-3-phenyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-propane-1,2-dione, 1c. Yield 60%; $[\alpha]_D^{27} = -52.3$ (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.35 (m, 2H), 7.26–7.20 (m, 3H), 4.51 (t, 1H, $J = 6.0$ Hz), 2.41 (br s, 3H), 2.28 (td, 1H, $J = 11.8$, 4.7 Hz), 2.04–1.99 (m, 4H), 1.52–1.46 (m, 1H), 1.42–1.37 (m, 1H), 1.17 (s, 3H), 1.15 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 195.9, 170.1, 158.3, 136.9, 128.6, 126.5, 122.2, 69.2, 59.1, 52.1, 46.9, 39.9, 28.3, 26.4, 26.1, 20.5, 19.7; HRMS (EI) calcd for $C_{19}H_{22}N_2O_3$ 326.1630. Found 326.1626; IR (neat, cm^{-1}): 2998, 2963, 2919, 1740, 1715, 1660, 1594, 1490, 1457, 1418, 1387, 1345, 1320, 1306, 1205, 1115, 968, 759; Crystal data for **1c** (colorless crystals, recrystallized from hexanes/EtOAc) at 25 °C: $C_{19}H_{22}N_2O_3$, M 326.396, orthorhombic, $P2_12_12_1$, $a = 10.1656$ (8) Å, $b = 11.6227$ (9) Å, $c = 15.2081$ (13) Å, $V = 1796.9$ (11) Å^3, $Z = 4$, $D_c = 1.206$ Mg/m^3, $\mu = 0.082$ mm^{-1}, 2518 reflections, 6858 parameters, $R = 0.0718$, $Rw = 0.1779$.

4.3.2. 1-(10,10-Dimethyl-2-oxo-3-phenyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-butane-1,2-dione, 1d. Yield 65%; $[\alpha]_D^{27} = -55.7$ (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.34 (m, 2H), 7.26–7.19 (m, 3H), 4.62 (m, 1H), 3.0 (br s, 1H), 2.66 (br s, 1H), 2.27 (td, 1H, $J = 11.8$, 5.4 Hz), 2.03–1.98 (m, 4H), 1.51–1.45 (m, 1H), 1.40–1.34 (m, 1H), 1.17 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 198.9, 170.0, 158.5, 137.0, 128.5, 126.4, 122.1, 69.0, 59.0, 52.0, 46.9, 39.6, 32.0, 28.3, 26.4, 20.4, 19.7, 6.9; HRMS (EI) calcd for $C_{20}H_{24}N_2O_3$ 340.1787. Found 340.1788; IR (neat, cm^{-1}): 2961, 1724, 1661, 1595, 1495, 1457, 1303, 1281, 1103, 1071, 970, 756, 692; Crystal data for **1d** (colorless crystal, recrystallized from hexanes/EtOAc) at 25 °C: $C_{20}H_{24}N_2O_3$, M 340.41, orthorhombic, $P2_12_12_1$, $a = 9.8270$ (5) Å, $b = 12.2890$ (7) Å, $c = 15.6450$ (10) Å, $V = 1889.35$ (19) Å^3, $Z = 4$, $D_c = 1.197$ Mg/m^3, $\mu = 0.081$ mm^{-1}, 6365 reflections, 227 parameters, $R = 0.0957$, $Rw = 0.1771$.

4.3.3. 1-(10,10-Dimethyl-2-oxo-3-phenyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-thiophen-2-yl-ethane-1,2-dione, 1e. Yield 82%; $[\alpha]_D^{27} = -268.9$ (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.80 (s, 1H), 7.38–7.35 (m, 4H), 7.21–7.17 (m, 2H), 4.59 (t, 1H, $J = 5.2$ Hz), 2.29 (td, 1H, J 12.0, 5.1 Hz), 2.17–2.13 (m, 1H), 2.03–1.93 (m, 3H), 1.54–1.48 (m, 1H), 1.41–1.34 (m, 1H), 1.20 (s, 3H), 1.15 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 179.5, 170.1, 158.0, 139.2, 137.5, 137.0, 136.8, 128.8, 128.6, 126.4, 121.8, 69.2, 59.2, 52.0, 47.1, 39.3, 28.4, 26.5, 20.6, 19.7; HRMS (EI) calcd for $C_{22}H_{22}N_2O_3S$ 394.1351. Found 394.1350; IR (neat, cm^{-1}): 3092, 3003, 2962, 1732, 1652, 1594, 1493, 1458, 1409, 1339, 1301, 1216, 1136, 1071, 1049, 753; Crystal data for **1e** (colorless crystals, recrystallized from hexanes/EtOAc) at 25 °C: $C_{22}H_{22}N_2O_3S$, M 394.48, orthorhombic, $P2_12_12_1$, $a = 10.1420$ (3) Å, $b = 12.3190$ (4) Å, $c = 16.3260$ (6) Å, $V = 2039.76$ (12) Å^3, $Z = 4$, $D_c = 1.285$ Mg/m^3, $\mu = 0.183$ mm^{-1}, 11172 reflections, 254 parameters, $R = 0.0755$, $Rw = 0.1394$.

4.3.4. 1-(10,10-Dimethyl-3,3-dioxo-3χ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-2-phenyl-ethane-1,2-dione, 1f. Yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, 2H, J 7.5 Hz), 7.66 (t, 1H, $J = 7.5$ Hz), 7.51 (t, 2H, $J = 7.5$ Hz), 4.07 (dd, 1H, $J = 7.8$, 4.8 Hz), 3.48 (d, 1H, $J = 13.8$ Hz), 3.42 (d, 1H, $J = 13.8$ Hz), 2.10–1.92 (m, 5H), 1.45 (t, 1H, $J = 9.0$ Hz), 1.35–1.33 (m, 1H), 1.20 (s, 3H), 0.97 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 186.9, 165.0, 135.1, 132.3, 130.2, 129.0, 64.4, 52.6, 50.0, 48.0, 45.1, 38.2, 32.9, 26.3, 21.0, 19.9; MS (EI) 347 $[M]^{+\cdot}$, $C_{18}H_{21}NO_4S$; Crystal data for **1f** (colorless crystals, recrystallized from hexanes/EtOAc) at 20 °C: $C_{18}H_{21}NO_4S$, M 347.42, orthorhombic, $P2_12_12_1$, $a = 7.6490$ (2) Å, $b = 11.7760$ (3) Å, $c = 19.0790$ (5) Å, $V = 1758.53$ (8) Å^3, $Z = 4$, $D_c = 1.343$ Mg/m^3, $\mu = 0.210$ mm^{-1}, 7515 reflections, 218 parameters, $R = 0.0883$, $Rw = 0.1495$.

4.4. For the experimental procedure for **1g–j**, see Ref. 9.

4.5. Typical procedure for the synthesis of 4-(2*S*)-(hydroxy-pent-4-enoyl)-10,10-dimethyl-3-phenyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one, 2a

The *N*-glyoxyloyl *N*-phenyl camphorpyrazolidinone **1a** (50 mg, 0.16 mmol) was dissolved in CH_3CN (2 mL) and $Eu(OTf)_3$ (96 mg, 0.16 mmol) and allyltributyltin (0.1 mL, 0.32 mmol) were added. The resulting mixture was stirred for 5 min at ambient temperature and quenched with H_2O (10 mL). The solution was extracted with CH_2Cl_2 (3 × 10 mL), the layers were separated and the organic extracts dried over anhydrous $MgSO_4$. The crude product was further purified by silica gel flash column chromatography eluted with hexane/EtOAc (1:1) to afford the total amount of products (51.05 mg, 90% yield), major diastereomer **2a**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.36 (m, 2H), 7.26–7.24 (m, 3H), 5.80–5.70 (m, 1H), 5.16 (m, 1H), 5.12 (m, 1H), 4.30 (dd, 1H, $J = 7.9$, 5.0 Hz), 4.05 (m, 1H), 2.81–2.75 (m, 1H), 2.53–2.47 (m, 1H), 2.40–2.26 (m, 2H), 2.11 (dd, 1H, $J = 13.5$, 7.9 Hz), 2.08–2.01 (m, 2H), 1.51–1.38 (m, 2H), 1.20 (s, 3H), 1.15 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 171.0, 169.1, 138.1, 132.7, 128.9, 126.8, 122.5, 118.7, 69.4, 68.5, 59.2, 52.2, 47.1, 38.9, 37.7, 28.9, 26.7, 20.4, 20.2; HRMS (EI) calcd for $C_{21}H_{26}N_2O_3$ 354.1943. Found 354.1939. Crystal data for **2a** (colorless crystals, recrystallized from hexanes/EtOAc) at 25 °C: $C_{21}H_{28}N_2O_4$, $M = 372.465$, orthorhombic, $P2_12_12_1$, $a = 9.6023$ (3) Å, $b = 11.7053$ (4) Å, $c = 17.4243$ (7) Å, $V = 1958.45$ (12) Å^3, $Z = 4$, $D_c = 1.263$ Mg/m^3, $\mu = 0.09$ mm^{-1}, 10744 reflections, 7839 parameters, $R = 0.0731$, $Rw = 0.1768$.

4.5.1. 4-(2*R*)-(Hydroxy-2-phenyl-pent-4-enoyl)-10,10-dimethyl-3-phenyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one, 2b. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.56 (m, 2H), 7.39–7.29 (m, 7H), 7.14 (1H, m), 5.62–5.55 (1H, m), 5.31 (dd, 1H, $J = 10.2$, 1.8 Hz), 5.26 (d, 1H, $J = 17.2$ Hz), 3.36 (dd, 1H, $J = 8.0$, 5.0 Hz), 3.17 (dd, 1H, $J = 13.4$,

6.1 Hz), 2.90 (s, 2H), 2.85–2.79 (m, 1H), 2.42 (dd, 1H, $J = 13.5$, 8.5 Hz), 2.14–2.04 (m, 1H), 1.99 (dd, 1H, $J = 13.5$, 8.0 Hz), 1.90–1.82 (m, 1H), 1.79 (t, 1H, $J = 4.0$ Hz), 1.04 (s, 3H), 1.01 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 176.2, 169.6, 139.7, 139.2, 132.7, 128.5, 128.3, 128.1, 124.9, 124.6, 122.2, 120.3, 78.4, 66.4, 59.5, 54.9, 48.7, 45.2, 42.1, 27.8, 26.8, 20.5, 19.9; HRMS (EI) calcd for $C_{27}H_{30}N_2O_3$ 430.2256. Found 430.2255; IR (neat, cm^{-1}): 3454, 2961, 1716, 1595, 1496, 1457, 1385, 1354, 1141, 1099, 1071, 922, 754; Crystal data for **2b** (colorless crystals, recrystallized from hexanes/EtOAc) at 25 °C: $C_{27}H_{30}N_2O_3$, M 430.53, orthorhombic, $P2_12_12_1$, $a = 8.8990$ (2) Å, $b = 10.8260$ (3) Å, $c = 24.2140$ (9) Å, $V = 2340.55$ (12) Å^3, $Z = 4$, $D_c = 1.222$ Mg/m^3, $\mu = 0.080$ mm^{-1}, 7840 reflections, 290 parameters, $R = 0.0653$, $Rw = 0.1225$.

4.5.2. 4-(2*S*)-(Hydroxy-2-methyl-pent-4-enoyl)-10,10-dimethyl-3-phenyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one, 2c. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.30 (m, 4H), 7.20–7.16 (m, 1H), 5.72–5.70 (m, 1H), 5.24 (dd, 1H, $J = 10.0$, 1.8 Hz), 5.18 (dd, 1H, $J = 17.1$, 1.8 Hz), 4.3 (dd, 1H, $J = 8.0$, 5.0 Hz), 2.76–2.73 (m, 1H), 2.68 (dd, 1H, $J = 6.7$, 3.8 Hz), 2.32–2.16 (m, 4H), 2.04–1.96 (m, 1H), 1.92 (t, 1H, $J = 3.9$ Hz), 1.46 (s, 3H), 1.45 (m, 1H), 1.39–1.32 (m, 1H), 1.14 (s, 3H), 1.10 (s, 3H); HRMS (EI) calcd for $C_{22}H_{28}N_2O_3$ 368.2100. Found 368.2106. Crystal data for **2c** (colorless crystals, recrystallized from hexanes/EtOAc) at 25 °C: $C_{22}H_{28}N_2O_3$, M 368.46, monoclinic, $P2_1$, $a = 8.8760$ (10) Å, $b = 11.2330$ (17) Å, $c = 10.9320$ (19) Å, $V = 1011.1$ (3) Å^3, $Z = 2$, $D_c = 1.210$ Mg/m^3, $\mu = 1.210$ mm^{-1}, 6214 reflections, 245 parameters, $R = 0.0955$, $Rw = 0.2180$.

4.5.3. 4-(2*S*)-(Ethyl-2-hydroxy-pent-4-enoyl)-10,10-dimethyl-3-phenyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one, 2d. Inseparable diastereomers; IR (neat, cm^{-1}): 3479, 2967, 2938, 2881, 1695, 1595, 1493, 1458, 1382, 1299, 1214, 918, 752.

4.5.4. 4-(2*S*)-(Hydroxy-2-thiophen-2-yl-pent-4-enoyl)-10,10-dimethyl-3-phenyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one, 2e. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.29 (m, 4H), 7.25–7.24 (m, 1H), 7.15–7.10 (m, 1H), 7.03 (dd, 1H, $J = 3.6$, 1.0 Hz), 6.98 (dd, 1H, $J = 4.8$, 3.6 Hz), 5.68–5.57 (m, 1H), 5.33–5.25 (m, 2H), 3.78 (dd, 1H, $J = 7.9$, 5.2 Hz), 3.18 (br s, 1H), 3.12 (dd, 1H, $J = 15.1$, 8.0 Hz), 2.80–2.74 (m, 1H), 2.65 (dd, 1H, $J = 13.5$, 8.0 Hz), 2.24–2.12 (m, 2H), 1.95–1.87 (m, 1H), 1.83 (t, 1H, $J = 4.1$ Hz), 1.26–1.20 (m, 2H), 1.06 (s, 3H), 1.04 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 175.2, 169.5, 144.9, 138.9, 131.9, 128.3, 127.4, 125.1, 125.0, 124.2, 122.4, 120.5, 77.9, 67.32, 59.6, 54.7, 48.7, 45.3, 42.3, 27.9, 26.8, 20.4, 19.9; HRMS (EI) calcd for $C_{16}H_{20}N_2O_3$ 436.1821. Found 436.1817. IR (neat, cm^{-1}): 3411, 3076, 3009, 2964, 2882, 1694, 1595, 1495, 1456, 1434, 1389, 1304, 1215, 1093, 754, 705.

4.5.5. 1-(10,10-Dimethyl-3,3-dioxo-3χ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-(2*R*)-hydroxy-2-phenyl-pent-4-en-1-one, 4f. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.54 (m, 2H), 7.37–7.33 (m, 2H), 7.29–7.26 (m, 1H), 5.79–5.70 (m, 1H), 5.23 (dd, 1H, $J = 16.8$, 1.0 Hz), 5.24 (dd, 1H, $J = 10.6$, 1.0 Hz), 4.02 (dd, 1H, $J = 7.6$, 4.8 Hz), 3.72 (s, 1H), 3.46 (d, 1H, $J = 13.5$ Hz), 3.41 (d, 1H, $J = 13.5$ Hz), 3.31 (dd, 1H, $J = 13.8$, 6.2 Hz), 2.63 (dd, 1H, $J = 13.8$, 8.2 Hz), 1.90 (dd, 1H, $J = 13.8$, 6.2 Hz), 1.87–1.85 (m, 1H), 1.70–1.68 (m, 1H), 1.65 (m, 1H), 1.35–1.27 (m, 2H), 0.87 (s, 3H), 0.73 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 174.2, 140.1, 132.3, 128.1, 127.8, 125.2, 121.2, 80.0, 67.6, 54.2, 48.2, 47.4, 44.7, 44.5, 38.4, 33.2, 26.3, 20.5, 19.8; MS (EI) 372 ([M−OH]$^{+\cdot}$, $C_{21}H_{27}NO_4S$); IR (neat, cm^{-1}): 3581, 2951, 2878, 1677, 1478, 1450, 1414, 1334, 1272, 1215, 1168, 1129, 1067; Crystal data for **4f** (colorless crystals, recrystallized from hexanes/EtOAc) at −73 °C: $C_{22}H_{30}N_2O_4SSi$, M 446.63, orthorhombic, $P2_1P2_1P2_1$, $a = 8.87220$ (2) Å, $b = 14.4130$ (3) Å, $c = 18.1900$ (5) Å, $V = 2286.67$ (9) Å^3, $Z = 4$, $D_c = 1.297$ Mg/m^3, $\mu = 0.224$ mm^{-1}, 14140 reflections, 272 parameters, $R = 0.0720$, $Rw = 0.1076$.

4.5.6. 1-(10,10-Dimethyl-3,3-dioxo-3χ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-(2*S*)-hydroxy-2-phenyl-pent-4-en-1-one, 5f. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.50 (m, 2H), 7.37–7.33 (m, 2H), 7.31–7.29 (m, 1H), 5.77–5.67 (m, 1H), 5.14 (dd, 1H, $J = 10.6$, 1.0 Hz), 5.10 (dd, 1H, J 16.8, 1.0 Hz), 4.31 (s, 1H), 4.00 (dd, 1H, $J = 7.7$, 4.9 Hz), 3.41 (d, 1H, $J = 13.6$ Hz), 3.28 (d, 1H, $J = 13.6$ Hz), 3.10 (dd, 1H, $J = 13.9$, 6.6 Hz), 2.62 (dd, 1H, $J = 13.9$, 7.7 Hz), 2.10–2.04 (dd, 1H, $J = 13.9$, 7.7 Hz), 1.96–1.84 (m, 4H), 1.37–1.33 (m, 2H), 1.16 (s, 3H), 0.94 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 174.4, 139.2, 132.5, 128.1, 128.0, 125.5, 120.1, 80.6, 67.1, 53.3, 48.8, 47.8, 47.7, 44.7, 38.9, 33.0, 26.4, 21.0, 19.9; MS (EI) 372 ([M−OH]$^{+\cdot}$, $C_{21}H_{27}NO_4S$); IR (neat, cm^{-1}): 3581, 2951, 2878, 1677, 1478, 1450, 1414, 1334, 1272, 1215, 1168, 1129, 1067; Crystal data for **5f** (colorless crystals, recrystallized from hexanes/EtOAc) at −73 °C: $C_{21}H_{27}NO_4S$, M 389.50, monoclinic, $P2_1$, $a = 8.6320$ (2) Å, $b = 11.4770$ (4) Å, $c = 10.2410$ (3) Å, $V = 997.72$ (5) Å^3, $Z = 2$, $D_c = 1.297$ Mg/m^3, $\mu = 0.188$ mm^{-1}, 7040 reflections, 249 parameters, $R = 0.0704$, $Rw = 0.1756$.

4.5.7. 4-(2*R*)-(Hydroxy-2-phenyl-pent-4-enoyl)-10,10-dimethyl-3-(toluene-4-sulfonyl)-3,4-diaza-tricyclo[5.2.1.0^{1,5}]-decan-2-one, 6g. $R_f = 0.54$ (2:1 hexanes/EtOAc); $[\alpha]_D^{27} = +142.0$ (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, 2H, $J = 8.0$ Hz), 7.54 (d, 2H, $J = 7.2$ Hz), 7.37 (d, 2H, $J = 8.0$ Hz), 7.33–7.26 (m, 3H), 5.92 (m, 1H), 5.35 (d, 1H, $J = 9.6$ Hz), 5.28 (d, 1H, $J = 16.8$ Hz), 3.34 (dd, 1H, $J = 13.2$, 5.5 Hz), 3.15 (s, 1H), 3.02 (s, 1H), 2.76–2.73 (m, 1H), 2.46 (s, 3H), 2.46–2.42 (m, 1H), 2.00–1.94 (m, 1H), 1.81–1.78 (m, 3H), 1.27 (s, 3H), 1.05 (s, 3H), 0.97–0.91 (m, 1H), 0.86–0.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 153.0, 144.8, 139.5, 136.0, 132.6, 129.3, 129.1, 128.4, 128.0, 124.7, 122.1, 78.4, 67.5, 59.0, 55.1, 49.5, 46.3, 41.5, 28.0, 26.2, 21.7, 20.7, 19.7; HRMS (EI) calcd for $C_{28}H_{32}N_2O_5S$ 509.2060. Found 509.2053; Crystal data for **6g** (colorless crystals, recrystallized from hexanes/EtOAc) at 20 °C: $C_{28}H_{32}N_2O_5S$, M 508.62, monoclinic, $P2_1$, $a = 8.6460$ (2) Å, $b = 11.5040$ (3) Å, $c = 13.4890$ (3) Å,

$V = 1301.10$ (5) Å^3, $Z = 2$, $D_x = 1.298$ Mg/m^3, $\mu = 0.165$ mm^{-1}, 4476 reflections, 326 parameters, $R = 0.0652$, $Rw = 0.1377$.

4.5.8. 4-(2*S*)-(Hydroxy-2-phenyl-pent-4-enoyl)-10,10-dimethyl-3-(toluene-4-sulfonyl)-3,4-diaza-tricyclo[5.2.1.0^{1,5}]-decan-2-one, 7g. $R_f = 0.46$ (2:1 hexanes/EtOAc); $[\alpha]_D^{27} = -71.3$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, 2H, $J = 7.8$ Hz), 7.67 (d, 2H, $J = 7.8$ Hz), 7.39–7.28 (m, 5H), 5.94 (m, 1H), 5.32 (d, 1H, $J = 10.1$ Hz), 5.26 (d, 1H, $J = 17.2$ Hz), 4.32 (t, 1H, $J = 6.2$ Hz), 3.27 (dd, 1H, $J = 13.4$, 6.2 Hz), 2.93 (br s, 1H), 2.66 (dd, 1H, $J = 13.4$, 8.4 Hz), 2.46 (s, 3H), 2.08–2.02 (m, 1H), 1.89–1.74 (m, 3H), 1.56 (s, 1H), 1.27–1.16 (m, 2H), 0.90 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 172.9, 145.2, 140.2, 135.6, 133.0, 129.5, 128.9, 128.1, 127.6, 125.4, 121.9, 78.7, 72.5, 60.3, 51.7, 51.1, 47.0, 39.5, 29.1, 26.5, 21.8, 20.2, 19.5; HRMS (EI) calcd for $C_{28}H_{32}N_2O_5S$ 508.2026. Found 508.2009; Crystal data for **7g** (colorless crystals, recrystallized from hexanes/EtOAc) at −73 °C: $C_{28}H_{32}N_2O_5S$, *M* 508.62, orthorhombic, $P2_12_12_1$, $a = 6.3790$ (2) Å, $b = 18.5760$ (6) Å, $c = 21.1690$ (8) Å, $V = 2508.45$ (15) Å^3, $Z = 4$, $D_x = 1.347$ Mg/m^3, $\mu = 0.172$ mm^{-1}, 4409 reflections, 326 parameters, $R = 0.1054$, $Rw = 0.1766$.

4.6. Typical procedure for the synthesis of 4-(2*S*)-(hydroxy-2-phenyl-acetyl)-10,10-dimethyl-3-phenyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one, 8b

Under a N_2 atmosphere, *N*-phenyl camphorpyrazolidinone phenylglyoxylate **1b** (100 mg, 0.26 mmol) was dissolved in dry THF (5 mL) at −78 °C. To this solution, K-Selectride (0.26 mL, 1.0 M solution in dry THF, 0.26 mmol) was added slowly. The reaction mixture was stirred for 2 h at −78 °C and quenched with H_2O (15 mL). The aqueous layer was extracted with ethyl acetate (3 × 15 mL), the organic layers separated, washed with saturated NaCl solution (10 mL) and dried over anhydrous $MgSO_4$. The organic layer was concentrated to a solid residue, which was purified by silica gel flash column chromatography using hexane/ethyl acetate (1:1) as the eluent to give the corresponding products as a colorless solid (99 mg, 98%), major diastereomer is **8b**. $[\alpha]_D^{22} = -11.5$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 7H), 7.2 (t, 1H, $J = 7.2$ Hz), 7.04 (d, 2H, $J = 7.2$ Hz), 5.04 (s, 1H), 4.16 (br s, 1H), 4.05 (t, 1H, $J = 6.7$ Hz), 2.75–2.72 (m, 1H), 2.25–2.11 (m, 2H), 2.02–1.98 (m, 2H), 1.33 (m, 2H) 1.07 (s, 3H), 0.91 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 171.2, 167.6, 138.2, 137.8, 129.0, 128.8, 128.7, 127.0, 126.5, 121.7, 72.3, 68.0, 59.3, 52.2, 47.0, 37.9, 28.7, 26.6, 20.3, 19.6; HRMS (EI) calcd for $C_{24}H_{26}N_2O_3$ 390.1938. Found 390.1945; IR (neat, cm^{-1}): 3462, 2947, 1703, 1659, 1488, 1454, 1320, 1303, 1091, 1052, 912, 724; Crystal data for **8b** (colorless crystals, recrystallized from hexanes/EtOAc) at 25 °C: $C_{24}H_{26}N_2O_3$, *M* 390.47, orthorhombic, $P2_12_12_1$, $a = 10.4410$ (3) Å, $b = 10.77760$ (3) Å, $c = 16.8250(6)$ Å^3, $Z = 4$, $D_c = 1.254$ Mg/m^3, $\mu = 0.083$ mm^{-1}, $R = 0.1187$, $Rw = 0.1875$.

4.6.1. 4-(2*S*)-(Hydroxy-propionyl)-10,10-dimethyl-3-phenyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one, 8c. $[\alpha]_D^{22} = -67.1$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.33 (m, 2H), 7.26–7.20 (m, 3H), 4.28 (dd, 1H, $J = 8.0$, 5.1 Hz), 4.08 (m, 1H), 2.83–2.77 (m, 1H), 2.33–2.26 (m, 1H), 2.10 (dd, 1H, $J = 13.7$, 8.0 Hz), 2.06–2.03 (m, 2H), 1.51–1.36 (m, 2H), 1.33 (d, 3H, $J = 6.6$ Hz), 1.21 (s, 3H), 1.16 (s, 3H). ^{13}C (100 MHz, $CDCl_3$) δ 171.7, 170.6, 138.4, 129.0, 126.7, 122.0, 77.7, 68.5, 66.0, 59.3, 52.3, 47.1, 37.3, 28.9, 26.7, 20.5, 20.3; HRMS (EI) calcd for $C_{19}H_{24}N_2O_3$ 328.1781. Found 328.1783; IR (neat, cm^{-1}): 3462, 2961, 1715, 1597, 1495, 1455, 1371, 1304, 1214, 1107, 1035, 756.

4.6.2. 4-(2*S*)-(Hydroxy-butyryl)-10,10-dimethyl-3-phenyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one, 8d. $[\alpha]_D^{22} = -27.1$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–736 (m, 2H) 7.25–7.22 (m, 3H) 4.29 (dd, 1H, $J = 7.8$, 5.2 Hz), 3.88 (br s, 1H), 3.01 (br s, 1H), 2.81–2.74 (m, 1H), 2.35–2.27 (m, 1H), 2.10 (dd, 1H, $J = 13.6$, 11.0 Hz), 2.07–2.02 (m, 2H), 1.82–1.73 (m, 1H), 1.54–1.40 (m, 3H), 1.2 (s, 3H), 1.15 (s, 3H), 0.94 (t, 3H, $J = 7.4$ Hz); ^{13}C (100 MHz, $CDCl_3$) δ 171.3, 169.8, 138.2, 128.9, 126.8, 122.5, 71.0, 68.5, 59.2, 52.1, 47.1, 37.5, 28.9, 27.6, 26.6, 20.4, 20.2, 9.7; HRMS (EI) calcd for $C_{20}H_{26}N_2O_3$ 342.1938. Found 342.1939; IR (neat, cm^{-1}): 3507, 2969, 2929, 2874, 1712, 1652, 1494, 1457, 1354, 1306, 1217, 1049, 758, 712; Crystal data for **8d** (colorless crystals, recrystallized from hexanes/EtOAc) at 25 °C: $C_{20}H_{27}N_2O_{3.5}$, *M* 351.44, orthorhombic, $P2_12_12_1$, $a = 10.45480$ (5) Å, $b = 10.7670$ (5) Å, $c = 16.0710$ (9) Å^3, $Z = 4$, $D_c = 1.290$ Mg/m^3, $\mu = 0.088$ mm^{-1}, $R = 0.1087$, $Rw = 0.2161$.

4.6.3. 4-(2*R*)-(Hydroxy-2-thiophen-2-yl-acetyl)-10,10-dimethyl-3-phenyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one, 8e. $[\alpha]_D^{22} = -10.2$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 3H), 7.25–7.17 (m, 3H), 7.04–7.0 (m, 2H), 5.28 (s, 1H), 4.06 (m, 2H), 2.74–2.72 (m, 1H), 2.22–2.18 (m, 1H), 2.2 (dd, 1H, $J = 12.8$, 8.2 Hz), 2.03 (m, 2H), 1.36–1.26 (m, 2H), 1.08 (s, 3H), 0.99 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 171.0, 167.0, 140.4, 138.1, 128.8, 127.0, 126.6, 126.5, 126.3, 121.9, 67.7, 67.6, 59.2, 52.5, 46.9, 38.0, 28.7, 26.7, 20.3, 19.5; HRMS (EI) calcd for $C_{22}H_{24}N_2O_3S$ 396.1502. Found 396.1501; IR (neat, cm^{-1}): 3434, 2992, 2958, 2924, 1712, 1667, 1491, 1457, 1371, 1329, 1306, 1217, 1080, 1046, 769, 713. Crystal data for **8e** (colorless crystals, recrystallized from hexanes/EtOAc) at 25 °C: $C_{22}H_{24}N_2O_3S$, *M* 396.49 orthorhombic, $P2_12_12_1$, $a = 10.5030$ (3) Å, $b = 11.5270(4)$ Å, $c = 16.7140$ (6) Å^3, $Z = 4$, $D_c = 1.301$ Mg/m^3, $\mu = 0.185$ mm^{-1}, $R = 0.1549$, $Rw = 0.3304$.

4.7. Typical procedure for the synthesis of 4-(2*S*)-(hydroxy-2-phenyl-acetyl)-10,10-dimethyl-3-(toluene-4-sulfonyl)-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one, 10g

Under a N_2 atmosphere, *N*-tosylcamphorpyrazolidinone phenylglyoxylate **1g** (200 mg, 0.43 mmol) was dissolved in dry THF (4 mL) at −78 °C. To this solution was added L-Selectride (0.86 mL, 1.0 M solution in THF, 0.86 mmol). The reaction mixture was stirred for

45 min at −78 °C and quenched with H_2O (25 mL). The aqueous layer was extracted with ethyl acetate (3 × 25 mL), the organic layers separated, washed with a saturated solution of NaCl (2 × 25 mL) and dried over anhydrous $MgSO_4$. The organic layer was concentrated to a solid residue, which was purified by silica gel flash column chromatography using hexane/ethyl acetate (2:1) as the eluent to give the corresponding product as a colorless solid (121 mg, 60%, major diastereomer is **10g**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (m, 1H), 7.53–7.52 (m, 2H), 7.44–7.37 (m, 5H), 5.30 (br s, 1H), 3.89 (br s, 1H), 3.50 (br s, 1H), 2.46 (s, 3H), 2.21–2.17 (m, 2H), 1.94 (m, 1H), 1.86 (m, 1H), 1.78 (dd, 1H, $J = 13.3$, 8.1 Hz), 1.25 (s, 2H), 1.19 (s, 3H), 1.10 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 175.6, 171.1, 145.2, 138.7, 135.9, 129.3, 128.9, 128.7, 127.8, 71.7, 66.3, 59.0, 54.9, 46.9, 39.4, 27.9, 26.2, 21.7, 20.2, 19.7; HRMS (FAB) $(M+H)^{+\cdot}$ calcd for $C_{25}H_{29}N_2O_5S$ 469.1797. Found 469.1805.

4.7.1. 4-(2*R*)-(Hydroxy-2-phenyl-acetyl)-10,10-dimethyl-3-(toluene-4-sulfonyl)-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one, 11g. Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, 2H, $J = 8.0$ Hz), 7.44 (d, 2H, $J = 7.0$ Hz), 7.40 (d, 2H, $J = 8.0$ Hz), 7.31–7.23 (m, 3H), 5.82 (br s, 1H), 4.17 (br s, 1H), 3.76 (dd, 1H, $J = 7.8$, 5.6 Hz), 2.52 (m, 1H), 2.48 (s, 3H), 1.78–1.74 (m, 3H), 1.65 (br s, 1H), 1.12–1.06 (m, 1H), 0.80 (s, 3H), 0.41 (m, 1H), 0.09 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 171.3, 146.8, 137.6, 134.2, 130.2, 129.5, 128.6, 128.5, 128.0, 72.0, 70.1, 60.4, 52.0, 47.5, 34.2, 29.6, 26.9, 21.8, 20.0, 18.5; HRMS (EI) $(M+H)^{+\cdot}$calcd for $C_{25}H_{29}N_2O_5S$ 469.1797. Found 469.1794. Crystal data for **11g** (colorless crystals, recrystallized from hexanes/EtOAc) at 25 °C: $C_{25}H_{28}N_2O_5S$, M 468.55 triclinic, *P1*, $a = 9.6500$ (2) Å, $b = 10.895$ (2) Å, $c = 12.9202$ (3) Å, $V = 1163.11$ (4) Å^3, $Z = 2$, $D_c = 1.338$ Mg/m^3, $\mu = 0.179$ mm^{-1}, 14805 reflections, 596 parameters, $R = 0.0585$, $Rw = 0.1430$.

4.7.2. 4-(2*R*)-(Hydroxy-butyryl)-10,10-dimethyl-3-(toluene-4-sulfonyl)-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one, 10i. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, 2H, $J = 7.0$ Hz), 7.39 (d, 2H, $J = 7.0$ Hz), 7.28 (s, 1H), 4.55 (br s, 1H), 3.91 (br s, 1H), 3.08 (br s, 1H), 2.73 (d, 1H, $J = 13.7$ Hz), 2.48 (s, 3H), 1.95–1.17 (m, 5H), 1.26–1.20 (m, 2H), 1.06 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 173.1, 146.5, 134.4, 130.0, 129.2, 71.0, 70.5, 60.5, 52.3, 47.6, 34.9, 29.6, 29.5, 26.8, 22.7, 20.3, 20.2, 9.8; HRMS (FAB) $(M+H)^{+\cdot}$ calcd for $C_{21}H_{29}N_2O_5S$ 421.1797. Found 421.1806.

4.7.3. 4-(2*S*)-(Hydroxy-2-thiophen-2-yl-acetyl)-10,10-dimethyl-3-(toluene-4-sulfonyl)-3,4-diaza-tricyclo[5.2.1.0^{1,5}]-decan-2-one, 10j. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, 2H, $J = 8.4$ Hz), 7.41 (d, 2H, $J = 8.4$ Hz), 7.24 (d, 1H, $J = 5.0$ Hz), 7.15 (d, 1H, $J = 3.2$ Hz), 6.91 (dd, $J = 5.0$, 3.2 Hz), 6.10 (br s, 1H), 4.06 (br s, 1H), 3.76 (dd, 1H, $J = 8.3$, 5.4 Hz), 2.58–2.54 (m, 1H), 2.49 (s, 3H), 1.86–1.79 (m, 3H), 1.75 (d, 1H, $J = 8.3$ Hz), 1.13–1.08 (m, 1H), 0.86 (s, 3H), 0.47 (m, 1H), 0.33 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 177.6, 170.2, 146.9, 140.5, 134.0, 130.2, 129.4, 127.4, 126.6, 126.3, 70.5, 67.7, 60.3, 52.1, 47.5, 34.2, 29.6, 26.8, 21.8, 20.1, 18.2; HRMS (FAB) $(M+H)^{+\cdot}$ calcd for $C_{23}H_{27}N_2O_5S_2$ 475.1361. Found 475.1357.

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References

1. Representative allylation references see: (a) Teo, Y.-C.; Tan, K.-T.; Loh, T.-P. *Chem. Commun.* **2005**, 1318–1320; (b) V Vilaivan, T.; Winotapan, C.; Banphavichit, V.; Shinada, T.; Ohfune, Y. *J. Org. Chem.* **2005**, *70*, 3464–3471; (c) Lu, J.; Hong, M.-L.; Ji, S.-J.; Loh, T.-P. *Chem. Commun.* **2005**, 1010–1012; (d) Lee, J.-Y.; Miller, J. J.; Hamilton, S. S.; Sigman, M. S. *Org. Lett.* **2005**, *7*, 1837–1839; (e) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 159–161; (f) Hirama, L. C.; Gamsey, S.; Knueppel, D.; Steiner, D.; DeLaTorre, K.; Singaram, B. *Tetrahedron Lett.* **2005**, *46*, 2315–2318; (g) Fernandes, R. A.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 735–738; (h) Kim, J. G.; Waltz, K. M.; Garcia, I. F.; Kwiatkowski, D.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 12580–12585.
2. Representative reduction references see: (a) Letondor, C.; Humbert, N.; Ward, T. R. *PNAS* **2005**, *102*, 4683–4687; (b) Chandrasekhar, S.; Hota, R. *Tetrahedron: Asymmetry* **2005**, *16*, 751–754; (c) Gosselin, F.; O'Shea, P. D.; Roy, S.; Reamer, R. A.; Chen, C.-Y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 355–358; (d) Ushio, H.; Mikami, K. *Tetrahedron Lett.* **2005**, *46*, 2903–2906; (e) Lapis, A. A. M.; Fatima, A. D.; Martins, J. E. D.; Costa, V. E. U.; Pilli, R. A. *Tetrahedron Lett.* **2005**, *46*, 495–498; (f) Schlatter, A.; Kundu, M. K.; Woggon, W.-D. *Angew. Chem., Int. Ed.* **2004**, *43*, 6731–6734; (g) Xu, J.; Wei, T.; Zhang, Q. *J. Org. Chem.* **2004**, *69*, 6860–6866; (h) Ohno, K.; Kataoka, Y.; Mashima, K. *Org. Lett.* **2004**, *6*, 4695–4697; (i) Xu, J.; Wei, T.; Zhang, Q. *J. Org. Chem.* **2003**, *68*, 10146–10151; (j) Nettles, S. M.; Matos, K.; Burkhardt, E. R.; Rouda, D. R.; Corella, J. A. *J. Org. Chem.* **2002**, *67*, 2970–2976.
3. (a) Keck, G. E.; Truong, A. P. *Org. Lett.* **2005**, *7*, 2149–2152; (b) Fatima, A. D.; Kohn, L. K.; Antonio, M. A.; Carvalho, J. E. D.; Pilli, R. A. *Bioorg. Med. Chem.* **2005**, *13*, 2927–2933; (c) Keck, G. E.; Yu, T.; McLawa, M. D. *J. Org. Chem.* **2005**, *70*, 2543–2550; (d) Atobe, M.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **2005**, *46*, 2669–2773; (e) Faiz, A. K.; Rashmirekha, S.; Jyotirmayee, D.; Savitha, G. *J. Org. Chem.* **2004**, *69*, 5295–5301; (f) Tosaki, S.-Y.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 495–498; (g) Ramachandran, P. V.; Liu, H.; Ram Reddy, M. V.; Brown, H. C. *Org. Lett.* **2003**, *5*, 3755–3757; (h) Ghosh, A. K.; Lei, H. *J. Org. Chem.* **2002**, *67*, 8783–8788; (i) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293; (j) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243–249.
4. (a) Scafato, P.; Leo, L.; Superchi, S.; Rosini, S. *Tetrahedron* **2002**, *58*, 153–159; (b) Loupy, A.; Monteux, D. A. *Tetrahedron* **2002**, *58*, 1541–1549; (c) Fukuzawa, S.-I.; Miura, M.; Matsuzawa, H. *Tetrahedron Lett.* **2001**, *42*,

4167–4169; (d) Shin, J. A.; Cha, J. H.; Pae, A. N.; Choi, K. I.; Koh, H. Y.; Kang, H.-Y. *Tetrahedron Lett.* **2001**, *42*, 5489–5492; (e) Bandopadhyaya, A. K.; Sangeetha, N. M.; Radha, A.; Maitra, U. *Tetrahedron: Asymmetry* **2000**, *11*, 3463–3466; (f) Kiegiel, K.; Jurczak, J. *Tetrahedron Lett.* **1999**, *40*, 1009–1012; (g) Chen, C.-J.; Chu, Y.-Y.; Liao, Y.-Y.; Tsai, Z.-H.; Wang, C. C.; Chen, K. *Tetrahedron Lett.* **1999**, *40*, 1141–1144; (h) Ghosh, A. K.; Chen, Y. *Tetrahedron Lett.* **1995**, *36*, 6811–6814; (i) Soai, K.; Ishizaki, M. *J. Org. Chem.* **1986**, *51*, 3290–3295; (j) Hanessian, S. *Total Synthesis of Natural Product: The Chiron Approach*; Pergamon Press: New York, 1983; Chapter 2.

5. Corey, E. J.; Yu, C.-M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495–5496.
6. (a) Vedejs, E.; Ahmad, S.; Larsen, S. D.; Westwood, S. J. *J. Org. Chem.* **1987**, *52*, 3937–3938; (b) White, J. M.; Ohira, S. *J. Org. Chem.* **1986**, *51*, 5492–5494; (c) Hanessian, S. *Total Synthesis of Natural Product: The Chiron Approach*; Pergamon Press: New York, 1983; Chapter 2.
7. (a) Fan, C. L.; Lee, W.-D.; Teng, N.-W.; Sun, Y.-C.; Chen, K. *J. Org. Chem.* **2003**, *68*, 9816–9818; (b) Sibi, M. P.; Liu, M. *Curr. Org. Chem.* **2001**, *5*, 719–755; (c) Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908–9909; (d) Adam, W.; Pastor, A.; Peters, K.; Peters, E.-M. *Org. Lett.* **2000**, *2*, 1019–1022; (e) Chu, Y.-Y.; Yu, C.-S.; Chen, C.-J.; Yang, K.-S.; Lain, J.-C.; Lin, C.-H.; Chen, K. *J. Org. Chem.* **1999**, *64*, 6993–6998; (f) Alvarez-Ibara, C.; Csaky, A. G.; Maroto, R.; Quiroga, M. L. *J. Org. Chem.* **1995**, *60*, 7934–7940.
8. (a) Pan, J.-F.; Venkatesham, U.; Chen, K. *Tetrahedron Lett.* **2004**, *45*, 9345–9347; (b) Wang, S.-G.; Tsai, H. R.; Chen, K. *Tetrahedron Lett.* **2004**, *45*, 6183–6185; (c) Lee, W.-D.; Chiu, C.-C.; Hsu, H.-L.; Chen, K. *Tetrahedron* **2004**, *60*, 6657–6664.
9. Chen, J.-H.; Venkatesham, U.; Lee, L.-C.; Chen, K. *Tetrahedron*, in press.
10. Christofers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591–4597.
11. (a) Bandini, M.; Cozzi, P. G.; Garelli, A.; Melchiorre, P.; Umani-Ronchi, A. *Eur. J. Org. Chem.* **2002**, 3243–3249; (b) Ooi, T.; Takahashi, M.; Maruoka, K. *J. Am. Chem. Soc.* **1996**, *118*, 11307–11308.
12. Similar seven-membered chelates were observed. See references: (a) Jurczak, J.; Prokopowicz, P. *Tetrahedron Lett.* **1998**, *39*, 9835–9838; (b) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1986**, *51*, 2609–2612.
13. **1b** (CCDC 286444), **1c** (CCDC 286443), **1d** (CCDC 286447), **1e** (CCDC 286446), **1f** (CCDC 286451), **1g** (CCDC 281384), **1j** (CCDC 281386), **2a** (CCDC 287868), **2b** (CCDC 247167), **2c** (CCDC 247166), **4f** (CCDC 286452), **5f** (CCDC 286450), **6g** (CCDC 281385), **7g** (CCDC 281388), **8b** (CCDC 286445), **8d** (CCDC 286447), **8e** (CCDC 287869), **11g** (CCDC 286453).