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FULL PAPER

Facile Access to Optically Active 2,6-Dialkyl-1,5-Diazacyclooctanes

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Abstract: The chiral substituted 1,5-diazacyclooctane (1,5-DACO) is of considerable importance and has attracted attention from a wide range of fields due to their unique chemical and biological properties. Despite the application potential, further study has not been optimized due to difficulties in their synthetic accessibility. Herewith, we reported that the 1,5-DACO bearing chiral auxiliary obtained from the formal [4+4] cycloaddition of *N*-alkyl-α,β-unsaturated imines can be further derivatized by nucleophilic alkylation to give various chiral substituted 1,5-DACO derivatives. The removal of the chiral auxiliary was effectively carried out using hydrogenation over Pearlman's catalyst. This methodology allows the production of a broad range of unprecedented optically active 2,6-dialkyl-1,5-DACO, which could not be accessed by other methods.

Introduction

Saturated nitrogen-containing heterocycles are an essential scaffold for numerous natural and synthetic molecules. They include compounds that may be used as drugs or synthons for the synthesis of other pharmacologically active substances. Of particular interest is compounds with 1,5-diazacyclooctane (1,5-DACO) moiety.[1] Several 1,5-DACO containing molecules such as (–)-sparteine,[2] (–)-cytisine,[3] Tröger's base,[4] (–)-(*S*,*S*)-homaline,[5] and SM-406[6] (see Figure 1a) have been widely applied in chemistry, biology, and the medical field. From the organic chemistry point of view, synthesis of the natural and unnatural 1,5-DACO containing molecules has been a challenging task, and over the past decades, chemists have attempted to accomplish a concise asymmetric synthesis of those kinds of molecules.[7] Typically, 1,5-DACO moiety has two electron lone pairs, which offer several attractive features for the molecules to be used as a framework for ligand development,[8] as demonstrated in the $(DACO)_2Ni^{II}$ and (1-alkyl-5-py-DACO)Cu^{II}-$OO^{\bullet}$ (see Figure 1a).[9] These complex ions have a strong ligand field, unique conformational requirements, and much space for further functionalization. Moreover, the flexible conformation of the 8-membered ring makes 1,5-DACO, and its derivatives become versatile templates for novel material synthesis.[10]

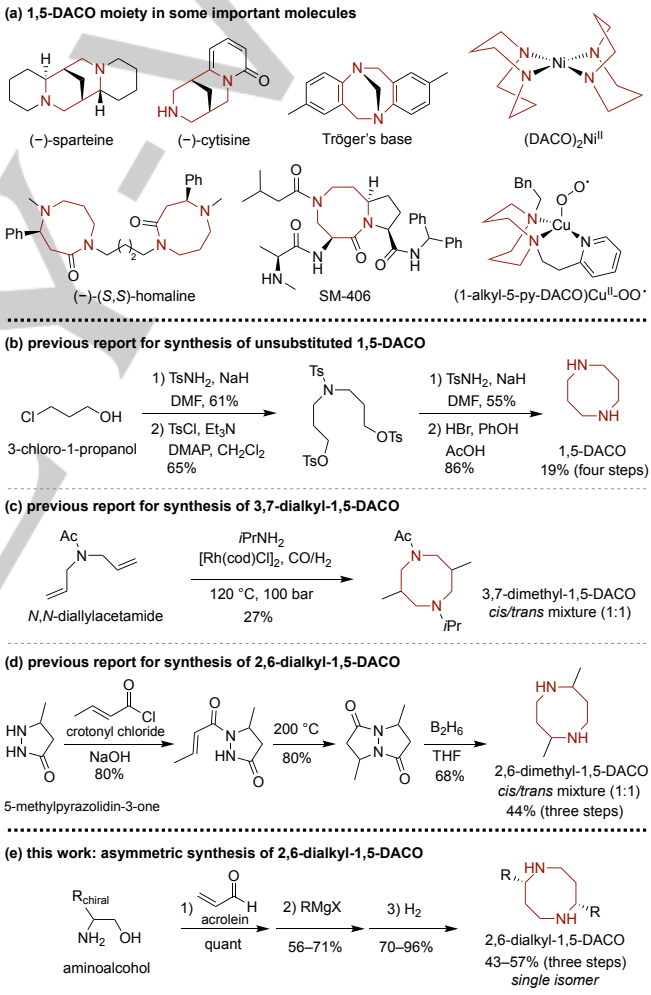

Figure 1. (a) Examples of 1,5-diazacyclooctane (1,5-DACO) based compounds. Natural alkaloids: (–)-sparteine, (–)-cytisine, and (–)-(*S*,*S*)-homaline. Synthetic compounds: Tröger's base and SM-406. Complex ions: $(DACO)_2Ni^{II}$ and (1-alkyl-5-py-DACO)Cu^{II}-$OO^{\bullet}$. [alkyl = 2-phenethyl; py = 2-(2-pyridyl)ethyl]. (b) Previous example for the synthesis of unsubstituted 1,5-DACO from 3-chloro-1-propanol in a 19% yield over four steps. (c) Previous example for the racemic synthesis of 3,7-dimethyl-1,5-DACO from *N*,*N*-diallylacetamide in a 27% yield. (d) Previous example for the racemic synthesis of 2,6-dimethyl-1,5-DACO in a 44% yield over three steps. (e) Our method for the asymmetric synthesis of various 2,6-dialkyl-1,5-DACO derivatives.

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Despite its potential application, the straightforward synthesis of chiral substituted 1,5-DACO remains challenging. An example of the synthesis of unsubstituted 1,5-DACO was reported by Börjesson (Figure 1b).[11] They reacted *p*-toluenesufonamide with 3-chloro-1-propanol to give a dialkylated product, which was subsequently tosylated, cyclized, and detosylated to give the unsubstituted 1,5-DACO in 19% yield over four steps. On the other hand, an example of a method that allows access to the 3,7-dialkyl-1,5-DACO was performed by utilizing Rh-catalyzed hydroformylation of dienes (Figure 1c).[12] However, this reaction only gives a low yield, and the product was obtained as a 1:1 mixture of the *cis* and *trans* isomers. Also, the preparation of 3,7-dialkyl-1,5-DACO by other methods reported in the literature are not satisfactory.[13]

On the contrary to the 3,7-dialkyl-1,5-DACO, there is only one example for the preparation of 2,6-dialkyl counterpart, which reported by Stetter in 1965 and improved later on by Kemp in 1979 (Figure 1d).[14] They utilized 5-methylpyrazolidin-3-one and crotonyl chloride to give an adduct, which subsequently heated to undergo cyclization. Subsequently, the diborane reduction of the cyclized product gives a 2,6-dialkyl-1,5-DACO. However, still, the product was obtained as a 1:1 mixture of the *cis* and *trans* isomers.

Herein, we utilize chiral aminoalcohol and acrolein to produce 8-membered heterocycles, which was then transformed by a simple functional group manipulation to the variously substituted chiral 2,6-dialkyl-1,5-DACO products (Figure 1e).

Results and Discussion

Previously, we reported that *N*-alkyl unsaturated imines derived from (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol and acrolein react rapidly through the formal [4+4] cycloaddition to give the corresponding 8-membered heterocycle **1** (Figure 2a). Also, we reported that the treatment of heterocycle **1** with lithium aluminum hydride ($LiAlH_4$) selectively reduced the hemiaminal function at C2 and C6 to give bis[*N*,*N*'-(2-indanolyl)]-1,5-DACO **2** in 92% yield.[15] We then, by utilizing a simple functional group manipulation, tested the potential for introducing stereoselectively additional alkyl groups to the C2 and C6 positions of heterocycle **1**. We achieve nucleophilic alkylation at C2 and C6 by reacting heterocycle **1** with methylmagnesium iodide to provide the chiral bis[*N*,*N*'-(2-indanolyl)]-2,6-dimethyl-1,5-DACO **3** (Figure 2a). However, despite the excellent diastereoselectivity, purification of the crude product allowed isolation of one diastereomer in only a 27% yield. Also, we found that removal of the chiral auxiliary, i.e., 2-indanol group, to give the free amine of 1,5-DACO is problematic. Hydrogenation of **3** over various palladium catalysts under various conditions failed to cleave the rigid structure of 1-amino-2-indanol with only starting material recovered. To our disappointment, the chiral auxiliary (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol only gave discouraging results, possibly due to their rigid structure, and was not suitable for this purpose.

However, despite the low reaction yield, we could unambiguously determine the stereochemistry of **3** by using X-ray crystallographic analysis (Figure 2b). Structure determination by single crystal X-ray diffraction identified **3** as chloroform solvate of bis[*N*,*N*'-(2-indanolyl)]-2,6-dimethyl-1,5-DACO hydrochloride salt derivative. According to the X-ray data, both the newly generated C2 and C6 stereogenic centers of 2,6-*cis*-isomer of **3** have (*R*) configurations. The proton is localized on one of the nitrogen atoms, i.e., N1 (see Figure 2b). The conformation of the 8-membered ring can be defined as a "distorted boat–distorted boat." Compound **3** in the crystal form a spiral along *a*-axis via O–H···Cl intermolecular hydrogen bonds.

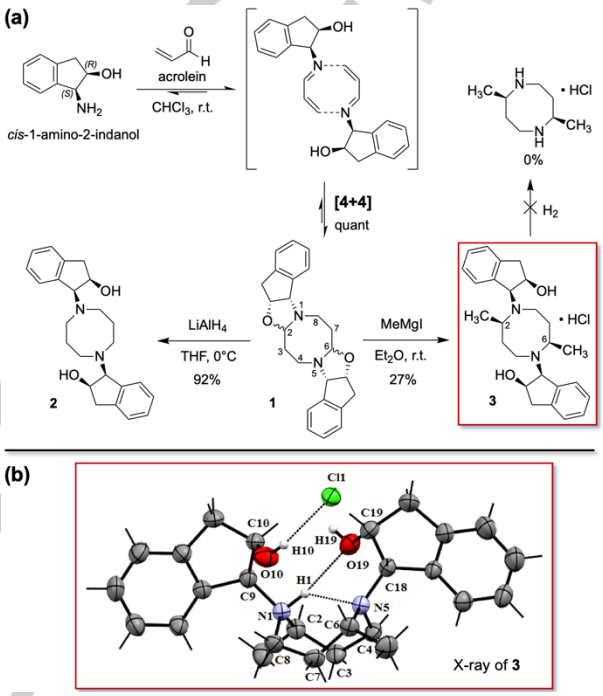

Figure 2. (a) Synthesis of 8-membered heterocycle **1** via the formal [4+4] cycloaddition of (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol and acrolein. Reduction of **1** by $LiAlH_4$ gave chiral bis[*N*,*N*'-(2-indanolyl)]-1,5-DACO **2** in 92% yield. Contrarily, alkylation of **1** by MeMgI gave chiral bis[*N*,*N*'-(2-indanolyl)]-2,6-dimethyl-1,5-DACO•HCl **3** in 27% yield. Attempt to cleave the 2-indanol group was not successful. (b) The absolute stereochemistry of C2 (*R*) and C6 (*R*) in the 2,6-*cis*-isomer of **3** were unambiguously determined by X-ray crystallographic analysis. Hydrogen bonds are marked with a dashed line.

Thus, our attention turned to a more flexible optically active aminoalcohol, i.e., (*R*)-(−)-2-phenylglycinol (Figure 3a), which previously has been employed as a useful chiral auxiliary in the synthesis of various substituted chiral 1,3-dialkyl-1,3-diaminopropanes.[16] The heterocycle **4** was readily prepared by mixing (*R*)-(−)-2-phenylglycinol and acrolein in chloroform at room temperature. The heterocycle **4** was obtained in quantitative yield as a 2:2:1 mixture of three diastereoisomers as evidenced by NMR spectroscopy (Figure 3a).[15a,17]

The transformation to the various chiral 2,6-dialkyl-1,5-DACO derivatives was then attempted (Figure 3a and Table 1). The method used in the transformation of heterocycle **1** to **3** (see Figure 2a) was then used to explore the potential for introducing alkyl groups stereoselectively at the C2 and C6 of heterocycle **4**. Nucleophilic alkylation at C2 and C6 was achieved by reacting **4**

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with methyl, ethyl, propyl, and isopropyl Grignard reagents to provide the chiral bis[*N*,*N*'-(2-phenylethanolyl)]-2,6-dialkyl-1,5-DACO **5a**–**5d** in 59–71% yields (Figure 3a and Table 1, Entry 1–4). Compared to the method that utilized (1*S*,2*R*)-(–)-*cis*-1-amino-2-indanol, the use of (*R*)-(–)-2-phenylglycinol as chiral auxiliary improves the yield of the reaction in this protocol. Herein, only one *cis* isomer was isolated, and another *cis* and *trans* isomers were not observed. Meanwhile, the reaction between heterocycle **4** with butyl and allyl Grignard reagents gives both major 2,6-*cis*- and minor 2,6-*trans*-isomers. Thus, we isolated **5e** and **5f** in 68% and 60% yields, respectively, with diastereoselectivity of ca. 10:3 ratio of *cis* to *trans* (see Table 1, Entry 5 and 6; and Supporting Information).

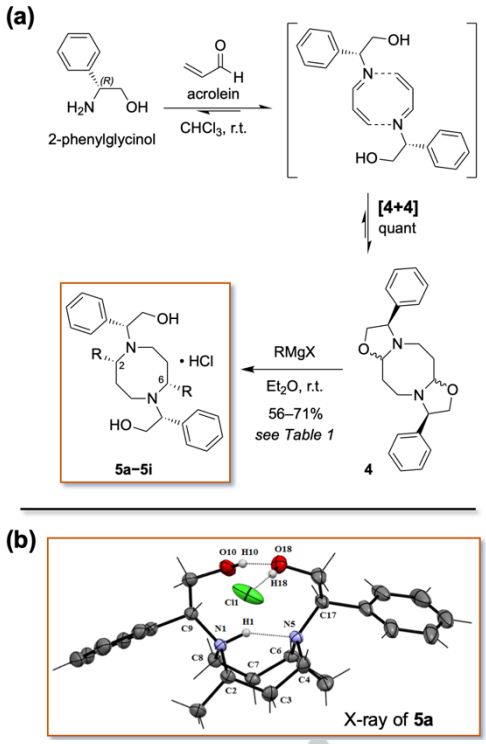

Figure 3. (a) Synthesis of 8-membered heterocycle **4** via the formal [4+4] cycloaddition of (*R*)-(–)-2-phenylglycinol with acrolein. Subsequently, alkylation of **4** by RMgX gives chiral bis[*N*,*N*'-(2-phenylethanolyl)]-2,6-dialkyl-1,5-DACO•HCl **5a**–**5i** (see Table 1 for details). (b) The absolute stereochemistry of C2 (*S*) and C6 (*S*) in the 2,6-*cis*-isomer of **5a** were unambiguously determined by X-ray crystallographic analysis. Hydrogen bonds are marked with a dashed line.

On the other hand, the reaction between heterocycle **4** with benzyl, vinyl, and phenyl Grignard reagents give the chiral bis[*N*,*N*'-(2-phenylethanolyl)]-2,6-dialkyl-1,5-DACO **5g**–**5i** in 56–67% yields (Table 1, Entry 7–9). In this case we observed only one *cis* isomer obtain from the reactions. It should be noted that the alkenyl-substituted chiral 1,5-DACO **5f** and **5h** (Table 1, Entry 6 and 8) can be utilized as synthetic precursors to the larger novel macrocyclic molecules, i.e., by ring-closing metathesis reaction, further highlighting the importance of this protocols. This method provides an efficient approach to synthesis the chiral 2,6-dialkyl-1,5-DACO derivatives. The stereochemistry produced through the alkylation, as listed in Table 1, was unambiguously determined using X-ray crystallographic analysis of compound **5a** (Figure 3b and Table 1, Entry 1), as well as ***trans*-5e** and ***trans*-5f** (see Table 1, Entry 5 and 6; and Supporting Information, Figure S1 and S2).

Previously, several attempts at using 2-phenylglycinol as chiral auxiliary to dictate the stereochemical outcome of nucleophilic reactions have been reported.[18] Herein, through a similar approach, the stereochemical outcome of the Grignard reactions listed in Table 1 was also mainly controlled by the (*R*)-(–)-2-phenylglycinol. The mechanism involves the formation of iminium ions, followed by the ring-opening of the hemiaminals, and the subsequent attack of the nucleophiles to the iminium ions from the less sterically hindered direction of the 8-membered ring. Also, although the detail is not yet apparent, we observed that different alkyl substituents affect the molecular properties of the 1,5-DACO; which include the decrease of diastereoselectivity when introducing a longer alkyl group (see Table 1, Entry 5 and 6), and the resistance during auxiliary removal of 2,6-dimethyl-1,5-DACO **5a** (*vide infra* and Table 2, Entry 1).

Table 1. Transformation of heterocycle **4** to chiral bis[*N*,*N*'-(2-phenylethanolyl)]-2,6-dialkyl-1,5-DACO•HCl **5a**–**5i**.

Entry	RMgX	Product	R	Isolated yield (*cis* isomer)
1[a]	MeMgI	**5a**	CH_3–	71%
2	EtMgBr	**5b**	CH_3CH_2–	62%
3	PrMgBr	**5c**	$CH_3CH_2CH_2$–	59%
4	*i*PrMgBr	**5d**	$(CH_3)_2CH$–	61%
5[b]	BuMgBr	**5e**	$CH_3CH_2CH_2CH_2$–	68%
6[c]	AllylMgBr	**5f**	CH_2=$CHCH_2$–	60%
7	BnMgBr	**5g**	$C_6H_5CH_2$–	58%
8	VinylMgBr	**5h**	CH_2=CH–	56%
9	PhMgBr	**5i**	C_6H_5–	67%

[a] The absolute stereochemistry of the 2,6-*cis*-isomer of **5a** was determined by X-ray crystallographic analysis (see Figure 3b). The absolute stereochemistry for the other compounds produced was assigned by the analogy of reaction stereochemical outcome to these compounds. [b] Both *cis* and *trans* isomers were observed and isolated in a 68:21 ratio. [c] Both *cis* and *trans* isomers were observed and isolated in a 60:17 ratio. The absolute stereochemistry of the ***trans*-5e** and ***trans*-5f** isomers were determined by X-ray crystallographic analysis (see Supporting Information, Figure S1 and S2).

Structure determination by single crystal X-ray diffraction identified bis[*N*,*N*'-(2-phenylethanolyl)]-2,6-dimethyl-1,5-DACO **5a** as hydrochloride salt derivative (Figure 3b). Both C2 and C6 chiral centers of the *cis*-isomer have (*S*) configuration, the 8-

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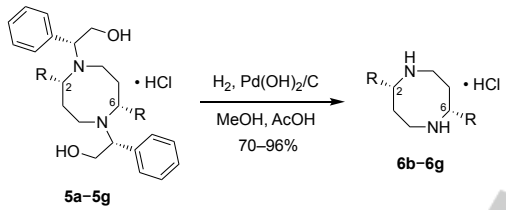
membered ring adopts the "boat–boat" conformation, and the methyl groups occupy equatorial positions. In the crystal **5a**, a strong intramolecular N–H···N bond was observed, as well as an intramolecular O–H···O bond. The joint implementation of these two interactions, apparently, leads to rigidity of the general conformation of the molecule **5a**, where C–N bonds become sterically shielded. Also, the NMR analysis of the obtained *cis* isomers of **5a**–**5i** showed that carbon atoms of C2 and C6; C3 and C7; C4 and C8; as well as the corresponding carbon atoms of two introduced substituents and two 2-phenylglycinol fragments are equivalent as they have the same chemical shift. As evidenced by ^{1}H NMR spectra, which display a singlet for the NH proton in the range of 13.2–15.6 ppm, suggested that the 2,6-disubstituted products **5a**–**5i** were obtained in their hydrochloride salt form. This result agreed well with the X-ray fluorescence (XRF) analysis, which confirmed the presence of chlorine in all isolated substances.

Table 2. Preparation of the chiral 2,6-dialkyl-1,5-diazacyclooctanes **6b**–**6g** by removal of the chiral auxiliary.



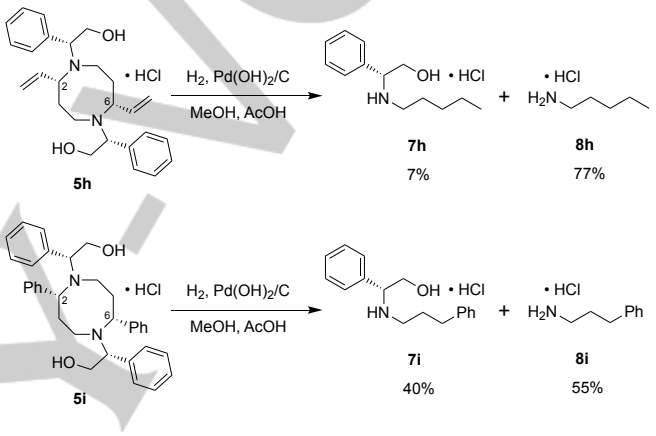
5a–5g **6b–6g**

Entry	Compound (*cis* isomer)	R–	Product (isolated yield)
1[a]	**5a**	CH_3–	–
2	**5b**	CH_3CH_2–	**6b** (90%)
3	**5c**	$CH_3CH_2CH_2$–	**6c** (96%)
4[b]	**5d**	$(CH_3)_2CH$–	**6d** (70%)
5	**5e**	$CH_3CH_2CH_2CH_2$–	**6e** (77%)
6[c]	**5f**	CH_2=$CHCH_2$–	**6c** (94%)
7	**5g**	$C_6H_5CH_2$–	**6g** (82%)

[a] Starting material **5a** was recovered quantitatively. [b] The absolute stereochemistry of (2*R*,6*R*)-2,6-diisopropyl-1,5-DACO•2HCl **6d** was confirmed by X-ray crystallographic analysis (Supporting Information, Figure S3). [c] Allyl substituent of **5f** underwent catalytic hydrogenolysis and was converted entirely to propyl group to give (2*S*,6*S*)-2,6-dipropyl-1,5-DACO•HCl **6c**.

Finally, the 2-phenylethanol group used as the chiral auxiliary was removed without incident by hydrogenolysis over Pearlman's catalyst in the presence of acetic acid in methanol. Thus, the hydrogenolysis of the *cis*-isomer of **5b**–**5g** gives the corresponding chiral 2,6-dialkyl-1,5-DACO **6b**–**6g** in 70–96% yields (Table 2, Entry 2–7). Under the reaction conditions, the hydrogenolysis of heterocycle **5f** was accompanied by hydrogenation of the allyl substituent to give (2*S*,6*S*)-2,6-dipropyl-1,5-DACO **6c** in 94% yield (Table 2, Entry 6). Structure analysis of (2*R*,6*R*)-2,6-diisopropyl-1,5-DACO **6d** by single crystal X-ray diffraction observed that the 8-membered ring in the crystal has a twist conformation (see Supporting Information, Figure S3).

Meanwhile, the hydrogenolysis of heterocycle **5a** did not proceed even under similar conditions, and only the starting material was recovered (Table 2, Entry 1). Although we could not rationale this phenomenon with absolute certainty, the X-ray analysis of **5a** (see Figure 3b), which revealed that the C–N bonds were sterically shielded (*vide supra*), might suggest the difficulty for hydrogenation to proceed.



Scheme 1. Hydrogenation of the *cis* isomers of **5h** and **5i** did not give the corresponding free amine compounds. Nevertheless, the vinyl substituent of **5h** completely converted to an ethyl group, and the 8-membered ring was cleaved at allyl fragments to give the acyclic amines **7h** and **8h**. Similarly, the 8-membered ring of **5i** was cleaved at benzyl fragments to give the acyclic amines **7i** and **8i**.

In the hydrogenolysis reactions of heterocycles **5h** and **5i**, which have 2,6-divinyl and 2,6-diphenyl substituents, respectively, the formation of the targeted cyclic products was not observed. Instead, the hydrogenolysis of heterocycle **5h** reduced the vinyl substituent and gave acyclic amines **7h** and **8h** in 7% and 77% yields, respectively (Scheme 1). Meanwhile, treatment of **5i** under similar conditions gives acyclic amines **7i** and **8i** in 40% and 55% yields, respectively (Scheme 1). The cleavage of carbon-nitrogen bonds in the 8-membered ring, which facilitated near the allyl and benzyl fragments of molecules **5h** and **5i**, can explain the formation of those acyclic amines. This phenomenon is consistent with the literature data for related systems.[19]

Conclusions

In contrast to the all-carbon-containing 8-membered ring, a well-studied class of compound,[20] the two-nitrogen-containing 8-membered ring vie for scarce attention due to difficulties in their synthetic accessibility. Herewith, we utilized the formal [4+4] cycloaddition of *N*-alkyl-α,β-unsaturated imines obtained from

acrolein and (*R*)-(−)-2-phenylglycinol to produce the 8-membered ring 1,5-DACO. Further treatment of the [4+4] cycloaddition product by nucleophilic alkylation, followed by hydrogenolysis, produced the various optically active 2,6-disubstituted-1,5-DACO derivatives. Although the method used two chiral auxiliaries, the simple procedure and high diastereoselectivity of the asymmetric reaction are advantageous for the synthesis of chiral disubstituted 1,5-DACO, a class of compound that has unique properties and high potentials for widespread application in various fields.

Experimental Section

General Experimental Procedures. All commercially available reagents were used without further purification. The preparative separation was performed by column chromatography on Silica gel 60A (Acros, 0.06-0.20 mm). Preparative thin-layer chromatography was performed on Merck PLC Silica gel 60 F_{254}, 1 mm. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 NMR spectrometer. Unless otherwise mentioned, $CDCl_3$ and CD_3OD were used as the solvents, and chemical shifts were represented as δ-values relative to the residual solvent peak. High-resolution mass spectrometry (HRMS) was recorded on a micrOTOF-Q III spectrometer. IR spectra were recorded on a Bruker Tensor-27 spectrometer fitted with a Pike MIRacle ATR accessory (diamond/ZnSe crystal plate). X-ray fluorescence spectra were obtained using an energy-dispersive X-ray spectrometer Shimadzu EDX 800HS2. Optical rotations were measured on a JASCO P-2200 polarimeter at the Sodium D-line (589 nm) and are reported as follows: [α] concentration (solvent, and *c* in g / 100 mL). The X-ray diffraction data for the single crystals of compound **3** were collected on a Bruker Smart Apex II CCD diffractometer; for the single crystals of **5a**, ***trans*-5e**, ***trans*-5f**, and **6d** were collected on a Bruker Kappa Apex CCD diffractometer using graphite monochromated Mo$K\alpha$ (0.71073 Å) radiation. The crystallographic data have been deposited in the Cambridge Crystallographic Data Centre. Deposition numbers CCDC-1937031 for compound **3**, CCDC-1937032 for compound **5a**, CCDC-1938847 for compound ***trans*-5e,** CCDC-1938848 for compound ***trans*-5f,** and CCDC-1937033 for compound **6d** contain the supplementary crystallographic data for this paper. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Preparation of bis[*N*,*N*'-(2-indanolyl)]-2,6-dimethyl-1,5-DACO•HCl (3). To a 1.0 M solution of methylmagnesium iodide in Et_2O (7.0 mL, 7.0 mmol, 10 eq), prepared from methyl iodide (0.65 mL, 10.5 mmol), magnesium turning (170 mg, 7.0 mmol) and Et_2O (7 mL) was added dropwise solution of heterocycle **1** (250 mg, 0.67 mmol, 1 eq) in Et_2O (10 mL) at ambient temperature. After the reaction mixture was refluxed under argon for 2 hours and stirred for another 2 hours at room temperature, saturated aqueous NH_4Cl solution (20 mL) was added and the resulting mixture was extracted with $CHCl_3$ (3×10 mL). The organic layers were combined, washed with water (50 mL), dried over Na_2SO_4, filtered, and concentrated to dryness under reduced pressure. The resulting crude mixture was purified using preparative thin layer chromatography [eluent: $CHCl_3$/MeOH (10:1)] to give the desired compound **3** as light-yellow solid (80 mg, 27%). R_f 0.19 ($CHCl_3$/MeOH 15:1); m.p. 180–195 °C (dec.); [α] = – 53.09 (CH_3OH, *c* = 1.00); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (d, $^3J_{H,H}$ = 6.7 Hz, 6H; C^9H_3, $C^{10}H_3$), 1.55–1.68, 2.12–2.26 (both m, 2H each; C^3H_2, C^7H_2), 2.74–2.86 (m, 2H; C^4H_2, C^8H_2), 2.96–3.14 (m, 4H; C^4H_2, C^8H_2, $C^{3'}H_2$, $C^{3''}H_2$), 3.27 (m, $^2J_{H,H}$ = – 16.8 Hz, $^3J_{H,H}$ = 7.7 Hz, 2H; $C^{3'}H_2$, $C^{3''}H_2$), 3.95–4.06 (m, 2H; C^2H, C^6H), 4.72 (d, $^3J_{H,H}$ = 7.7 Hz, 2H; $C^{1'}H$, $C^{1''}H$), 4.95 (ddd, $^3J_{H,H}$ = 7.7 Hz, 2H; $C^{2'}H$, $C^{2''}H$), 7.15–7.38 ppm (m, 8H, H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.65 (C^9, C^{10}), 31.23 (C^3, C^7), 39.83 ($C^{3'}$, $C^{3''}$), 41.82 (C^4, C^8), 61.08 (C^2, C^6), 71.19 ($C^{2'}$, $C^{2''}$), 71.83 ($C^{1'}$, $C^{1''}$), 125.98, 127.10, 127.13, 129.71, 135.87, 143.11 ppm (C_{arom}); IR (ATR): ν_{max} 3257 br, 2961, 2926, 2855, 1604, 1478, 1459, 1262, 1056, 739 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{35}ClN_2O_2$+H$^+$–HCl: 407.2693 [*M*+H–HCl]$^+$; found: 407.2695.

Representative procedure for nucleophilic alkylation: Preparation of bis[*N*,*N*'-(2-phenylethanolyl)]-2,6-dimethyl-1,5-DACO•HCl (5a). To a 1.0 M solution of methylmagnesium iodide in Et_2O (10.0 mL, 10.0 mmol, 10 eq), prepared from methyl iodide (0.93 mL, 15.0 mmol), magnesium turning (240 mg, 10.0 mmol) and Et_2O (10 mL) was added dropwise solution of heterocycle **4** (350 mg, 1.0 mmol, 1 eq) in Et_2O (12 mL) at ambient temperature. After the reaction mixture was refluxed under argon for 2 hours and stirred for another 2 hours at room temperature, saturated aqueous NH_4Cl solution (20 mL) was added and the resulting mixture was extracted with $CHCl_3$ (3×10 mL). The organic layers were combined, washed with water (30 mL), dried over Na_2SO_4, filtered, and concentrated to dryness under reduced pressure. The resulting residue was re-dissolved in a mixture of 2N HCl (10 mL) and $CHCl_3$ (10 mL). After mixing, the phases are allowed to separate and the aqueous phase is removed. The aqueous layer was extracted again with $CHCl_3$ (3×10 mL). The organic layers were combined, washed with water (40 mL), dried over Na_2SO_4, filtered, and concentrated to dryness under reduced pressure. The resulting crude product was purified using preparative thin layer chromatography [eluent: $CHCl_3$/MeOH (15:1)] to give the desired compound **5a** as light-yellow solid (300 mg, 71%). R_f 0.23 ($CHCl_3$/MeOH 15:1); m.p. 210–220 °C (dec.); [α] = + 6.11 ($CHCl_3$, *c* = 1.00); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.46 (d, $^3J_{H,H}$ = 6.2 Hz, 6H; C^9H_3, $C^{10}H_3$), 1.74–2.04 (m, 4H; C^3H_2, C^7H_2), 3.12–3.26 (m, 2H; C^4H_2, C^8H_2), 3.75 (dd, $^2J_{H,H}$ = – 12.4 Hz, $^3J_{H,H}$ = 4.5 Hz, 2H; $C^{2'}H_2$, $C^{2''}H_2$), 3.95 (td, $^3J_{H,H}$ = 12.1 Hz, $^2J_{H,H}$ = – 5.4 Hz, 2H; C^4H_2, C^8H_2), 4.07–4.28 (m, 4H; C^2H, C^6H, $C^{2'}H_2$, $C^{2''}H_2$), 4.66 (dd, $^3J_{H,H}$ = 12.4 Hz, $^3J_{H,H}$ = 4.5 Hz, 2H; $C^{1'}H$, $C^{1''}H$,), 6.82 (br, 2H; OH), 7.32 (s, 10H; H_{arom}), 15.30 ppm (s, 1H; NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.79 (C^9, C^{10}), 31.58 (C^3, C^7), 40.28 (C^4, C^8), 59.60 (C^2, C^6), 60.90 ($C^{2'}$, $C^{2''}$), 69.66 ($C^{1'}$, $C^{1''}$), 129.14, 129.23, 129.46, 134.38 ppm (C_{arom}); IR (ATR): ν_{max} 3237 br, 2972, 2925, 2877, 1581, 1488, 1450, 1090, 770, 705 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{24}H_{35}ClN_2O_2$+H$^+$–HCl: 383.2693 [*M*+H–HCl]$^+$; found: 383.2698.

Representative procedure for auxiliary cleavage: Preparation of (2*S*,6*S*)-2,6-diethyl-1,5-DACO•HCl (6b). A solution of bis[*N*,*N*'-(2-phenylethanolyl)]-2,6-diethyl-1,5-DACO **5b** (130 mg, 0.29 mmol) and Pearlman's catalyst (200 mg, 0.29 mmol) in a mixture of methanol (5 mL) and acetic acid (0.34 mL, 5.8 mmol) was stirred for 7 days under hydrogen atmosphere at ambient temperature. The catalyst was removed by filtration through Celite and washed with a mixture solution of acetic acid (0.4 mL) in methanol (40 mL). The filtrate was evaporated to dryness under reduced pressure. The crude product was purified using preparative thin layer chromatography [eluent: $CHCl_3$/MeOH (8:1)] to give the desired compound **6b** as colourless oil (53 mg, 90%). R_f 0.47 ($CHCl_3$/MeOH 5:1); [α] = + 13.48 (CH_3OH, *c* = 1.00); ^{1}H NMR (400 MHz, CD_3OD): δ = 1.01 (t, $^3J_{H,H}$ = 7.5 Hz, 6H; $C^{10}H_3$, $C^{12}H_3$), 1.58–1.75 (m, 6H; C^9H_2, $C^{11}H_2$, C^3H_2, C^7H_2), 2.05–2.16 (m, 2H; C^3H_2, C^7H_2), 3.01–3.13 (m, 4H; C^4H_2, C^8H_2, C^2H, C^6H), 3.28–3.43 ppm (m, 2H; C^4H_2, C^8H_2, including CH_3OH); ^{13}C NMR (100 MHz, CD_3OD): δ = 10.57 (C^{10}, C^{12}), 27.98 (C^9, C^{11}), 28.32 (C^3, C^7), 44.77 (C^4, C^8), 60.21 ppm (C^2, C^6); IR (ATR): ν_{max} 3380 br, 2963, 2933, 2875, 2851, 2740, 1624, 1593, 1461, 1382 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{10}H_{23}ClN_2$+H$^+$–HCl: 171.1856 [*M*+H–HCl]$^+$; found: 171.1856.

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Keywords: saturated heterocycles • diazacyclooctane • chiral amine • [4+4] cycloaddition • asymmetric synthesis

[1] a) H. D. Perlmutter, A. R. Katritzky, in *Adv. Heterocycl. Chem., Vol. 46* (Ed.: A. R. Katritzky), Academic Press, **1989**, pp. 1-72; b) G. Cirrincione, P. Diana, in *Comprehensive Heterocyclic Chemistry III* (Eds.: A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor), Elsevier, Oxford, **2008**, pp. 303-474.

[2] a) P. Karrer, F. Canal, K. Zohner, R. Widmer, *Helv. Chim. Acta* **1928**, *11*, 1062-1084; b) G. R. Clemo, R. Raper, C. R. S. Tenniswood, *J. Chem. Soc.* **1931**, 429-437; c) B. T. Smith, J. A. Wendt, J. Aubé, *Org. Lett.* **2002**, *4*, 2577-2579.

[3] L. A. Pabreza, S. Dhawan, K. J. Kellar, *Mol. Pharmacol.* **1991**, *39*, 9-12.

[4] a) B. Dolenský, J. Elguero, V. Král, C. Pardo, M. Valík, in *Adv. Heterocycl. Chem., Vol. 93* (Ed.: A. R. Katritzky), Academic Press, **2007**, pp. 1-56; b) Ö. V. Rúnarsson, J. Artacho, K. Wärnmark, *Eur. J. Org. Chem.* **2012**, *2012*, 7015-7041.

[5] a) O. Lefebvre-Soubeyran, *Acta Cryst. B* **1976**, *32*, 1305-1310; b) L. Crombie, D. Haigh, R. C. F. Jones, A. R. Mat-Zin, *J. Chem. Soc., Perkin Trans. 1* **1993**, 2055-2068.

[6] a) Y. Peng, H. Sun, Z. Nikolovska-Coleska, S. Qiu, C.-Y. Yang, J. Lu, Q. Cai, H. Yi, S. Kang, D. Yang, S. Wang, *J. Med. Chem.* **2008**, *51*, 8158-8162; b) Q. Cai, H. Sun, Y. Peng, J. Lu, Z. Nikolovska-Coleska, D. McEachern, L. Liu, S. Qiu, C.-Y. Yang, R. Miller, H. Yi, T. Zhang, D. Sun, S. Kang, M. Guo, L. Leopold, D. Yang, S. Wang, *J. Med. Chem.* **2011**, *54*, 2714-2726.

[7] a) B. T. O'Neill, D. Yohannes, M. W. Bundesmann, E. P. Arnold, *Org. Lett.* **2000**, *2*, 4201-4204; b) J.-P. R. Hermet, M. J. McGrath, P. O'Brien, D. W. Porter, J. Gilday, *Chem. Commun.* **2004**, 1830-1831; c) A. R. Pradipta, K. Tanaka, *Heterocycles* **2013**, *87*, 2001-2014; d) C. S. Hampton, M. Harmata, *Tetrahedron* **2016**, *72*, 6064-6077.

[8] a) Y. Goldberg, H. Alper, *Tetrahedron Lett.* **1995**, *36*, 369-372; b) D. Hoppe, T. Hense, *Angew. Chem. Int. Ed.* **1997**, *36*, 2282-2316; c) H. Wu, X.-m. Chen, Y. Wan, L. Ye, H.-q. Xin, H.-h. Xu, C.-h. Yue, L.-l. Pang, R. Ma, D.-q. Shi, *Tetrahedron Lett.* **2009**, *50*, 1062-1065; d) J. Rouden, M.-C. Lasne, J. Blanchet, J. Baudoux, *Chem. Rev.* **2014**, *114*, 712-778.

[9] a) W. K. Musker, H. S. Hussain, *Inorg. Chem.* **1966**, *5*, 1416-1419; b) D. K. Mills, J. H. Reibenspies, M. Y. Darensbourg, *Inorg. Chem.* **1990**, *29*, 4364-4366; c) W. K. Musker, *Coord. Chem. Rev.* **1992**, *117*, 133-157; d) T. Tano, Y. Okubo, A. Kunishita, M. Kubo, H. Sugimoto, N. Fujieda, T. Ogura, S. Itoh, *Inorg. Chem.* **2013**, *52*, 10431-10437; e) T. Abe, Y. Morimoto, T. Tano, K. Mieda, H. Sugimoto, N. Fujieda, T. Ogura, S. Itoh, *Inorg. Chem.* **2014**, *53*, 8786-8794; f) T. Abe, Y. Hori, Y. Shiota, T. Ohta, Y. Morimoto, H. Sugimoto, T. Ogura, K. Yoshizawa, S. Itoh, *Commun. Chem.* **2019**, *2*, 12.

[10] F. Ishiwari, N. Takeuchi, T. Sato, H. Yamazaki, R. Osuga, J. N. Kondo, T. Fukushima, *ACS Macro Lett.* **2017**, *6*, 775-780.

[11] a) L. Börjesson, C. J. Welch, *Acta Chem. Scand.* **1991**, *45*, 621-626; b) For the first synthesis of unsubstituted 1,5-DACO, see C. C. Howard, W. Marckwald, *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 2038-2042.

[12] Christian L. Kranemann, P. Eilbracht, *Eur. J. Org. Chem.* **2000**, *2000*, 2367-2377.

[13] a) R. Koliński, H. Piotrowska, T. Urbański, *J. Chem. Soc.* **1958**, 2319-2322; b) D. A. Cichra, H. G. Adolph, *Synthesis* **1983**, 830-833; c) P. R. Dave, F. Forohar, T. Axenrod, L. Qi, C. Watnick, H. Yazdekhasti, *Tetrahedron Lett.* **1994**, *35*, 8965-8968; d) P. R. Dave, F. Forohar, T. Axenrod, K. K. Das, L. Qi, C. Watnick, H. Yazdekhasti, *J. Org. Chem.* **1996**, *61*, 8897-8903; e) P. Livant, A. W. Majors, T. R. Webb, *J. Org. Chem.* **1996**, *61*, 3061-3069.

[14] a) H. Stetter, K. Findeisen, *Chem. Ber.* **1965**, *98*, 3228-3235; b) D. S. Kemp, M. D. Sidell, T. J. Shortridge, *J. Org. Chem.* **1979**, *44*, 4473-4476.

[15] a) K. Tanaka, R. Matsumoto, A. R. Pradipta, Y. Kitagawa, M. Okumura, Y. Manabe, K. Fukase, *Synlett* **2014**, *25*, 1026-1030; b) K. Fujiki, K. Tanaka, *Synthesis* **2018**, *50*, 1097-1104.

[16] A. R. Pradipta, K. Tanaka, *Bull. Chem. Soc. Jpn.* **2016**, *89*, 337-345.

[17] R. Noel, M. C. Fargeau-Bellassoued, C. Vanucci-Bacque, G. Lhommet, *Synthesis* **2008**, 1948-1954.

[18] a) L. Guerrier, J. Royer, D. S. Grierson, H. P. Husson, *J. Am. Chem. Soc.* **1983**, *105*, 7754-7755; b) T. K. Chakraborty, G. V. Reddy, K. A. Hussain, *Tetrahedron Lett.* **1991**, *32*, 7597-7600; c) L. E. Burgess, A. I. Meyers, *J. Org. Chem.* **1992**, *57*, 1656-1662; d) T. Inaba, I. Kozono, M. Fujita, K. Ogura, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2359-2365; e) K. Higashiyama, H. Inoue, H. Takahashi, *Tetrahedron* **1994**, *50*, 1083-1092; f) H. P. Husson, J. Royer, *Chem. Soc. Rev.* **1999**, *28*, 383-394; g) T. Yamauchi, H. Fujikura, K. Higashiyama, H. Takahashi, S. Ohmiya, *J. Chem. Soc., Perkin Trans. 1* **1999**, 2791-2794; h) E. Poupon, N. Kunesch, H. P. Husson, *Angew. Chem. Int. Ed.* **2000**, *39*, 1493-1495; i) E. Poupon, D. Francois, N. Kunesch, H. P. Husson, *J. Org. Chem.* **2004**, *69*, 3836-3841.

[19] I. D. Entwistle, W. W. Wood, in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 955-981.

[20] a) W. C. Still, I. Galynker, *Tetrahedron* **1981**, *37*, 3981-3996; b) E. Vedejs, W. H. Dent, D. M. Gapinski, C. K. Mcclure, *J. Am. Chem. Soc.* **1987**, *109*, 5437-5446; c) S. L. Schreiber, D. B. Smith, G. Schulte, *J. Org. Chem.* **1989**, *54*, 5994-5996.

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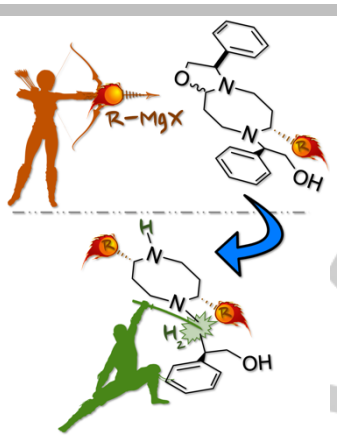
Entry for the Table of Contents

FULL PAPER

The 1,5-diazacyclooctane (1,5-DACO) obtained from formal [4+4] cycloaddition reaction of *N*-alkyl-α,β-unsaturated imines can be transformed to chiral substituted 1,5-DACO derivatives via nucleophilic alkylation, followed by hydrogenolysis. This method provides useful and facile access to various optically active 2,6-dialkyl-1,5-DACO, which might have unique chemical or biological properties.



Dilyara R. Chulakova, Ambara R. Pradipta, Olga A. Lodochnikova, Danil R. Kuznetsov, Kseniya S. Bulygina, Ivan S. Smirnov, Konstantin S. Usachev, Liliya Z. Latypova, Almira R. Kurbangalieva,* and Katsunori Tanaka**

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Facile Access to Optically Active 2,6-Dialkyl-1,5-Diazacyclooctanes