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The Novel *Cis*- and *Trans*- Isomerism of α-Monosubstituted Cyclododecanone Derivatives

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Abstract: The [3333]-2-one conformation is the preferred conformation of cyclododecanone and carbonyl is vertical to the near ring plane. To explore the stereochemistry of substituted cyclododecanone is beneficial to understanding their stability, reactivity and structure-activity relationships of these compounds. The *cis*- and *trans*- isomerism of the macrocyclic ketones based on the carbonyl orientation was not reported up to now. In order to confirm this isomerism, the novel *cis*- and *trans*- isomerism were theoretically observed based on the carbonyl orientation analysis in the [3333]-2-one conformation of cyclododecanone, and the *cis*- and *trans*- isomers of the α-monosubstituted cyclododecanones were practically synthesized, their structures were characterized by ^{1}H, ^{13}C NMR, HR-MS spectral data and X-ray diffraction analysis. This kind of *cis*- and *trans*- isomerism was first postulated and confirmed in the macrocyclic ketones using the α-monosubstituted cyclododecanone derivatives as the representatives.

Keywords: *cis*- and *trans*- Isomerism, α-Monosubstituted Cyclododecanone, Synthesis, X-ray Diffraction

1. Introduction

The stereochemistry of macrocyclic compounds is complicated because of the ring atom number, chiral center, functional groups and their preferred conformation. However, the relative rigid conformations were observed for the simple even and odd number macrocyclic alkanes and ketones in their solids and solutions, and these results were reviewed [1-4]. For example, [3232]-2-one, [3333]-2-one, [4343]-2-one and [4444]-2-one conformations were the preferred conformations in their solid states for cyclodecan- one, cyclododecanone, cyclotetradecanone and cyclohexade-canone, respectively. Due to the easily availability in the commercial market, most researches were focused on the utility of cyclododecanone and its derivatives as the starting materials or a recyclable protecting group [5-15]. Lots of cyclododecanone derivatives and its ring-enlargement products were also prepared, and their biological activities were evaluated for agrochemical application in our laboratory [16-21]. In order to gain insights into the structure-activity relationships of these compounds, the conformational analysis of cyclododecanone derivatives were carried out, found that most of compounds took [3333]-2-one preferred conformation, while some of them took low energy [3324]-2-one, [3423]-2-one or [4323]-3-one conformation because of the bulky hindrance of the substituted groups and π-π electron effect between the aromatic and carbonyl groups (Figure 1, A, B, C and D) [22-32]. As indicated in A, B and C in the Figure 1, there are α-corner-*syn*, α-corner-*anti*, α-side-*endo* and α-side-*exo* four type α-protons in the [3333]-2-one, [3324]-2-one and [3423]-2-one conformations of cyclododecanone (only α-side-*endo* and α-side-*exo* two type α-protons in the [4323]-3-one conformation) because the carbonyl orientation was vertical to the near ring plane [33-36]. When the α-protons were replaced by the substituted groups, the side-*endo* proton was most difficult to replace because the conformation with the side-*endo* group was a forbidden conformation [33]. The α-corner-*syn* proton was reported to easily replace in different kinds of reactions [37], and the α-corner-*syn* substituted products were stable in their solutions and solid states, they also could converse to the most stable α-side-*exo* substituted products when the groups were bulky hindrance or aryl groups [32, 33]. To the best of our knowledge, the α-corner-*anti* substituted cyclododecanone

had the similar stability as the α-side-*exo* substituted cyclododecanone [32], however the only one example of the α-corner-*anti* substituted cyclododecanone was the self-aldol product of cyclododecanone in our previous report [23] till to 2006. So far, our endeavor to obtain the α-corner-*anti* substituted cyclododecanone by the other kind of reaction was not success. In this case, the aldol reaction of cyclododecanone with the other aromatic aldehyde was utilized, and found that the products showed the significant α-corner-*anti* selectivity. Then, the *cis*- (α-corner-*syn*) and *trans*- (α-corner-*anti*) isomers were synthesized through substitution and aldol reaction, and confirmed by the X-ray diffraction of *cis*- and *trans*- α-corner-monosubstituted cyclododecanones, which were based on the carbonyl orientation. This kind of *cis*- and *trans*- isomerism based on the carbonyl orientation in the macrocyclic ketone compounds was first observed and reported through the α-corner monosubstituted cyclododecanone as the representative of macrocycles. The results were reported in this paper.

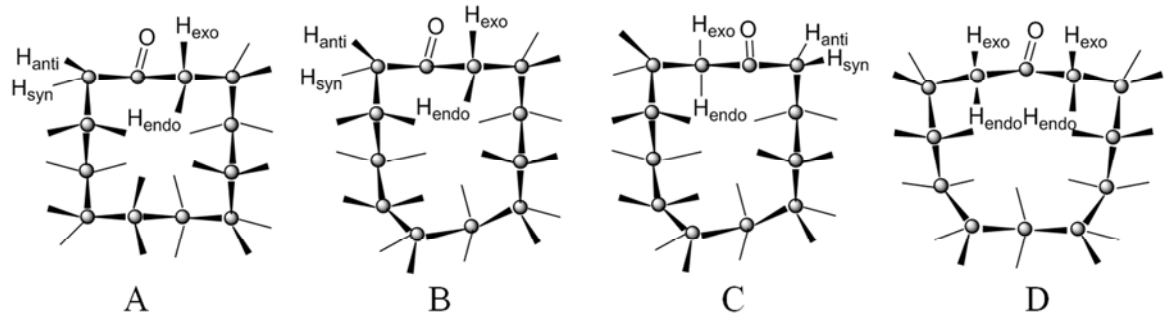


Figure 1. *[3333]-2-one, [3324]-2-one, [3423]-2-one and [4323]-3-one conformation of cyclododecanone [1].*

2. Results and Discussion

2.1. The Cis- and Trans- Isomerism of Cyclododecanone Derivatives Related with the Carbonyl Orientation

As we mentioned in the introduction, the conformation with the α-side-*endo* group was a forbidden conformation, and the conformation having the α-side-*exo* group could converse to the conformation with the α-corner-*syn* group in the solution, so we discussed the conformation case only having the α-corner groups in this paper. As indicated in the Figure 2, the α-corner-substituted cyclododecanone was divided into two relative configurations in the projection of the most favored [3333]-2-one conformation when used the orientation of carbonyl as the standard [33, 34], among of which the α-corner-*syn* substituted cyclododecanone was defined as a *cis*- isomer because the carbonyl and substituted groups (R) were in the same side of the ring plane (Figure 2, A and D), the α-corner-*anti* substituted cyclododecanone was defined as a *trans*- isomer because the carbonyl and substituted groups (R) were in the different side of the ring plane (Figure 2, B and C). The conformations A and D, the conformations B and C were mirror image relationship, they should be two pair of enantiomers, respectively. This phenomenon was not observed and reported in the small cycloketone derivatives because the carbonyl orientation was in the near ring plane. The α-corner-*syn* proton is difficult to transfer to the α-corner-*anti* proton through C_2- and Cs-pseudorotation of cyclododecanone because of its big energy barriers of 34.7 and 36.4 KJ/mol [1, 38], so the α-corner-*syn* substituted group (*cis*- isomer) is much more difficult to transfer to the α-corner-*anti* substituted group (*trans*- isomer) due to the much higher energy barrier in the similar pathway when the α-corner proton of cyclododecanone is replaced with the substituted group. The *cis*- and *trans*- isomers of the α-corner- monosubstituted derivatives should be obtained in different approaches according to above analysis. However, the *cis*- isomer (α-corner-*syn* monosubstituted cyclododecanone, Figure 2, A or D) was afforded and characterized using X-ray diffraction analysis in several chemical reactions [32-34, 39, 40], the only one example of the *trans*- isomer (α-corner-*anti* substituted cyclododecanone) was the self-aldol product of cyclododecanone in our previous report [23]. In order to confirm this *cis*- and *trans*- isomerism of the α-corner-monosubstituted cyclododecanone, how to prepare the *trans*- isomers of the α-corner-monosubstituted cyclododecanone derivatives challenge us for a long time.

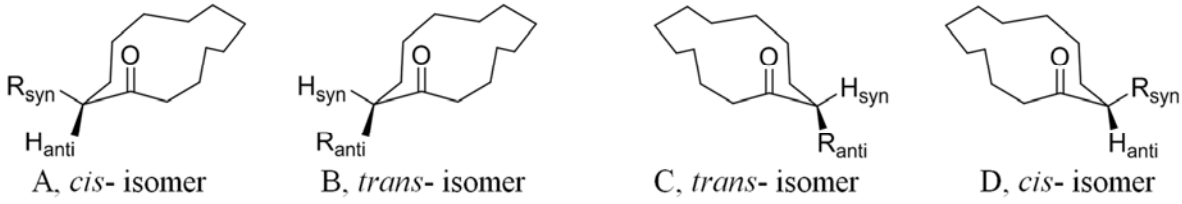


Figure 2. *The cis- and trans- isomerism of the α-corner-monosubstituted cyclododecanone derivatives.*

2.2. The Synthesis and Structures of the Cis- and Trans-Isomers of α-corner- Monosubstituted Cyclododecanones

The *cis*- (α-corner-*syn*) isomers 1a-1f were readily synthesized following the procedures in literatures [22, 27, 28, 33, 39] using cyclododecanone with benzyl chloride, 4-chloromethylpyridine and 2-chloromethylfuran or ethyl benzoate, ethyl isonicotinate and ethyl furan-2-carboxylate as the starting materials under the condition of NaH as the base (Figure 3). Their structures were confirmed by the ^{1}H, ^{13}C NMR, HR-ESI-MS data and X-ray diffraction of 1a, among of them, the ^{1}H, ^{13}C NMR data of 1a and 1d were identical with those in the previous reports [33, 39]. The X-ray structure of 1a as the representative was depicted in Fig. 3, which confirmed that the benzyl was located at the α-corner-*syn* position of [3333]-2-one conformation, which was consistence with the previous reports [33], and it is a *cis*-isomer based on the abovementioned defination.

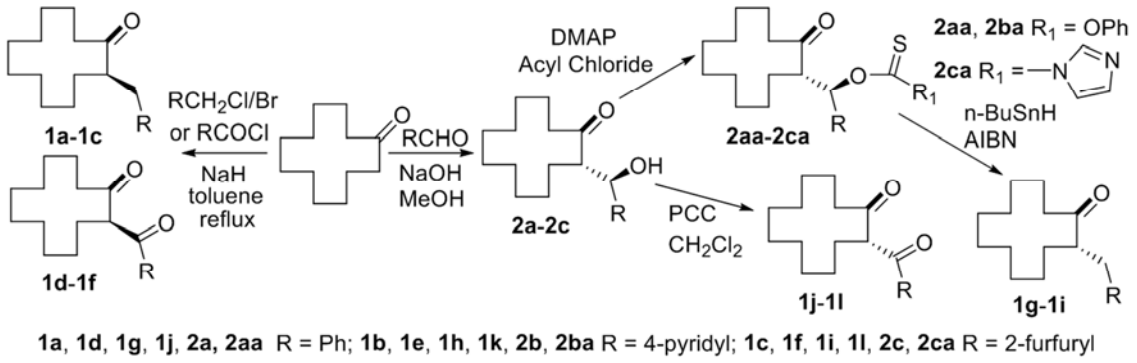


Figure 3. *Synthesis of the cis-(corner-syn) and trans-(corner-anti) isomers of α-monosubstituted cyclododecanones.*

As we know, the self-aldol product of cyclododecanone is the only one example of the α-corner-*anti* monosubstituted cyclododecanone in our previous report till 2006 [23]. After that, the aldol condensation of cyclododecanone with the benzaldehyde was also reported to produce 2-phenylmethyl-ene cyclododecanone or 2-phenyl hydroxymethyl cyclododecanone in different conditions under reflux temperature (Figure 4) [41-43], and the X-ray crystal structure of main product 2-phenyl hydroxymethyl cyclododecanone was clearly determined to be *anti*-aldol products, but they did not mention the relative configuration between the side chain group at the α-corner position and carbonyl [41]. We carefully analyzed the X-ray crystal structure of 2-phenyl hydroxymethyl cyclododecanone and found that the α-corner-substituted cyclododecanone have the α-corner-*anti* relative configuration between the side chain group and carbonyl, which was similar to the self-aldol product of cyclododecanone [23]. In this situation, the aldol products of cyclododecanone with the benzaldehyde and the other aromatic aldehyde could be used to prepare the *trans*- (α-corner-*anti* monosubstituted cyclododecanone) isomers 1g-1l through oxidation and reduction reaction of hydroxyl in the 2-aromatic hydroxymethyl cyclododecanone 2a-2c without change of α-corner-*anti* substitution (Figure 3).

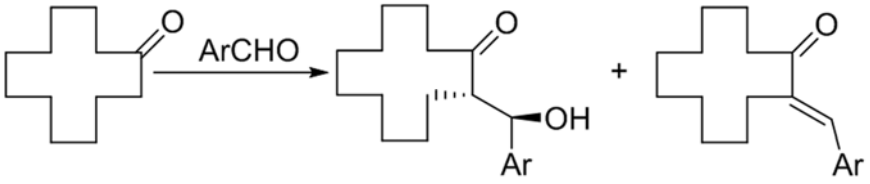


Figure 4. *The anti-aldol reaction of cyclododecanone with the benzaldehyde reported in literature [40].*

The aldol reaction of cyclododecanone with benzaldehyde, isonicotinaldehyde and furan-2-carbaldehyde was performed and afforded the α-corner-*anti* isomers 2a-2c in the base solution [23, 41]. Most importantly, one of the aldol reaction products 2c was selected to grow the crystal, and analyzed through X-ray diffraction. The result in Figure 7 clearly indicated that the 2-(furan-2-yl)hydroxymethyl was located at the α-corner-*anti* position of [3333]-2-one conformation, which was in agreement with that of the self-aldol and the other aldol products of cyclododecanone [23, 41]. The α-corner-*anti* selectivity of [3333]-2-one conformation could be rationalized as Figure 5, in which the base is difficulty to approach the corner-*syn* proton because the hindrance as well as hydrogen-bond between solvent methanol and carbonyl, so the base approaches the corner-*anti* proton from the less hindrance in space. Then the carbon cation attacked aldehyde to form the aldol product, and the *anti*-aldol selectivity in literature was also rationalized according to the antiperi-planar preferred conformation and intramolecular hydrogen-bond between hydroxyl and carbonyl groups of the aldol product [41]. In fact, the dihedral angels of H*syn*-C_2-C_{13}-H_{13}, C_1-C_2-C_{13}-C_{14} and C_3-C_2-C_{13}-O_2 in the crystal structure of 2c

were 178.70°, 179.22°, and 179.04°, respectively, which was in agreement with that of the local antiperiplanar preferred conformation. Then, 2a-2c was transferred to their esters 2aa-2ca. Initially, we try to prepare the similar ester 2cb as 2aa and 2ba using the same acyl chloride, but the unexpected compound 2cc was obtained. When the reaction was carried out from ambient temperature to 0°C, the compound 2cc was also obtained. The rational reason was that *O*-phenyl carbonochloridothioate was very active as electrophilic reagent, the electrophilic substitutent in the furan ring of ester 2cb and 1,5-shift of the proton took place, finally oxidation by air to afford compound 2cc (Figure 6). Finally, we replaced *O*-phenyl carbonochloridothioate with 1*H*-imidazole-1-carbothioyl chloride, and compound 2ca was obtained successfully.

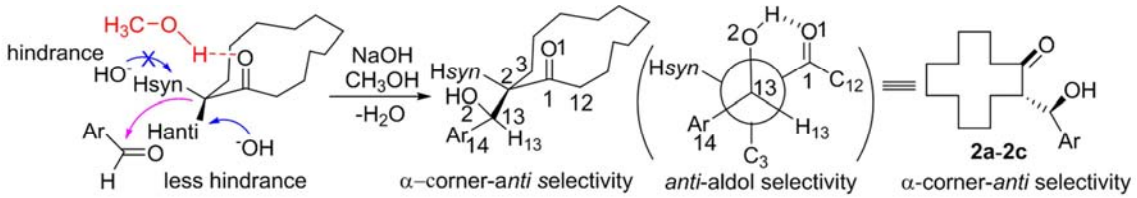


Figure 5. *The possible mechanism of α-corner-anti selectivity (anti-aldol selectivity) aldol products.*

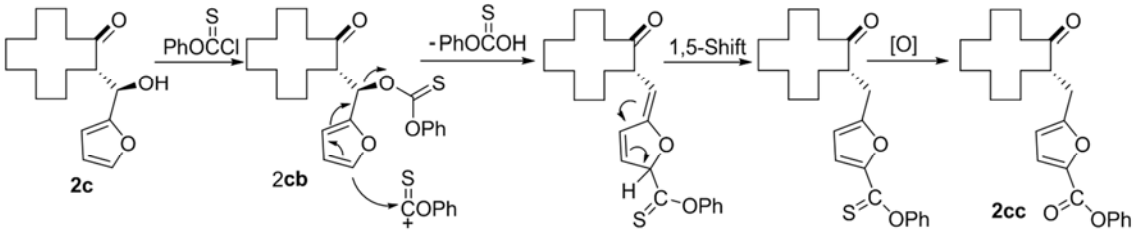


Figure 6. *Proposed possible forming mechanism of byproduct 2cc.*

Then, these esters 2aa-2ca were further reduced by *n*-BuSnH/AIBN [44, 45] in toluene at reflux temperature to afford compounds 1g-1i. The direct oxidization of 2a-2c with PCC [46, 47] produced compounds 1j-1l (Figure 3). All of new compounds were characterized by ^{1}H, ^{13}C NMR and high resolution mass spectral data. In these transformation processes, the relative configuration of α-carbon did not change, the position of the substituted groups in the [3333]-2-one conformation of compounds 1g-1l should be remained unchanged. In fact, the good crystals of 1h and 1k were obtained from their *n*-hexane or *n*-hexane/alcohol solutions, and their X-ray structures were depicted in Figure 7. The results unambiguously indicated that the 4-pyridylmethyl and isonicotinyl groups were located at the α-corner-*anti* position of [3333]-2-one conformation as that of 2c. From the above results, the configurational *cis*- and *trans*- (α-corner-*syn* and α-corner-*anti*) isomers of α-monosubstituted cyclododecanones were first obtained and confirmed through experimental data. For comparison, the characteristic differences of these isomers were listed in Table 1. The data in Table 1 showed that their melting points were significantly different, the typical ^{1}H and ^{13}C NMR chemical shifts were very similar, but also significantly different (Table 1, Figure 8). For example, the ^{13}C NMR chemical shifts of pyridine ring at δ 149.78 and 149.10 were observed in the ^{13}C NMR spectrum of 1b, while the ^{13}C NMR chemical shift of pyridine ring only at δ 149.67 was observed in the ^{13}C NMR spectrum of 1h due to completely overlapping of peaks. All of these results further indicated they were different compounds. As indicated in the introduction, this kind of configurational *cis*- and *trans*- (α-corner-*syn* and α-corner-*anti*) isomerism in cyclododecanone derivatives might be extended to the cyclodecanone, cyclotetradecanone and cyclohexadecanone analogs, which have similar ring skeleton [3232]-2-one, [4343]-2-one and [4444]-2-one conformation as [3333]-2-one of cyclododecanone.

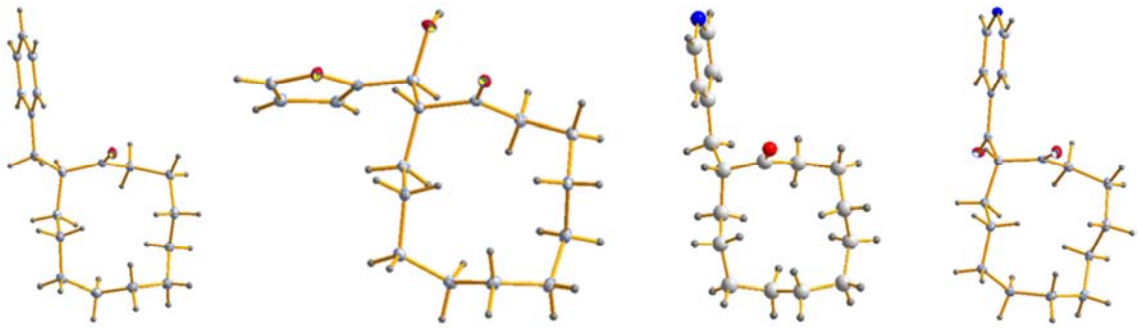
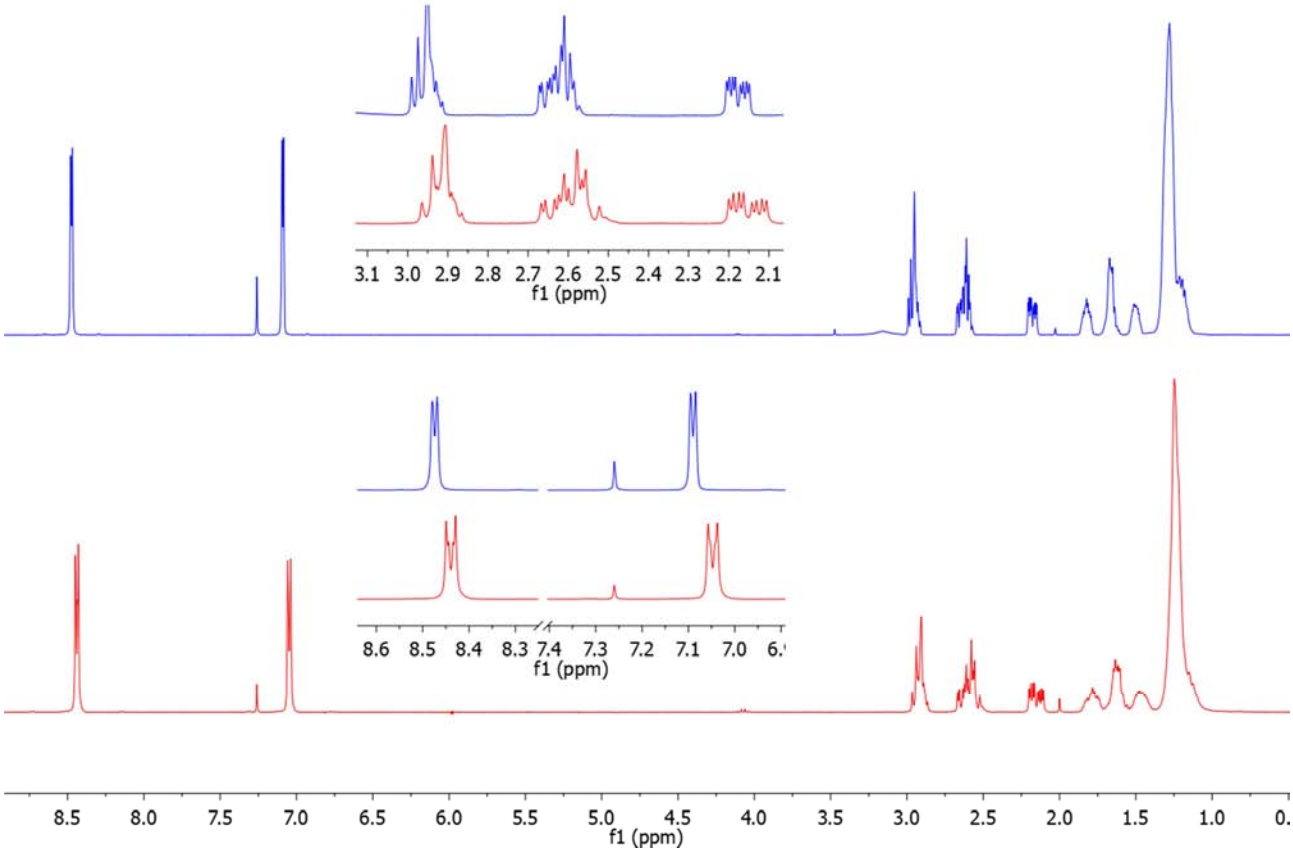


Figure 7. *The X-ray structures of compounds 1a, 2c, 1h and 1k.*

Meyers reported an asymmetric synthesis of (*R*)- and (*S*)-2-methyl cyclododecanone through (*E*)- and (*Z*)-lithioenamine under kinetic metalation and thermodynamic metalation conditions with 80% and 60% ee values [48], and (*R*)- isomer with 95% and 96% ee values was also prepared by enzymatic hydrolysis or Cu-catalyzed enantioselective conjugate addition [49, 50], but they did not show the relative configuration between methyl and carbonyl. It was very interesting that the characteristic methyl doublet of (*R*)-isomer is δ 0.97, (*S*)- isomer δ 1.05 in $CDCl_3$ in one report [48], but (*R*)- isomer is δ 1.06 in $CDCl_3$ in the other report [49]. These results are contradictory if the vertical orientation of carbonyl to the near ring planer is ignored, the chemical shifts of the (*R*)- and (*S*)- enantiomers should be the same in a non-chiral solvent condition. We primarily concluded that Meyers preparred the *cis*- and *trans*- isomers of 2-methyl cyclododecanone with certain of ee values, because the preferred ring conformation of (*E*)- and (*Z*)- twelve-membered enamine probably determined the *cis*- and *trans*-selectivity, the absolute configuration of chiral amine provided the enantioselectivity. The chemical shifts of the *cis*- and *trans*- isomers should be different, the (*S*)- and (*R*)-isomers in Meyers and Luchaco-Cullis papers [48, 49] should have the same relative configuration. Based on the above analysis, the synthesis and chiral resolution of *cis*- and *trans*-isomers of more α-corner-monosubstituted cyclododecanones and the other macrocycloalkanones are required and challenged, but they are under way in our laboratory.

Table 1. *The typical differences of the cis- and trans- isomers of the α-monosubstituted cyclododecanones* ***1a-1l****.*

R	Compd.	M. P (°C)	δ of ^{1}H NMR	δ of ^{13}C NMR
Ph	1a	68-70(69-71[33])	7.22-7.05(Ph); 2.89-2.80(α-H)	214.26(CO); 139.99, 128.95, 128.50, 126.26(Ph), 53.39(C_2);
	1g	55-57	7.30-7.14(Ph); 2.95-2.88(α-H)	214.33(CO); 140.04, 128.99, 128.54, 126.30(Ph); 53.43(C_2);
4-Pyridyl	1b	80-82	8.45; 7.04(Py); 2.93-2.90(α-H)	212.72(CO); 149.78, 149.10, 124.22(Py); 52.33(C_2);
	1h	73-75	8.47; 7.08(Py); 2.98-2.93(α-H)	212.86(CO); 149.67, 149.67, 124.47(Py); 52.49(C_2);
2-Furfuryl	1c	43-45	7.29; 6.26; 5.99(Fu); 3.06-3.01(α-H)	213.57(CO); 153.73, 141.23, 110.25, 106.23(Fu); 50.39(C_2);
	1i	35-37	7.33; 6.29; 6.03(Fu); 3.14-3.05(α-H)	213.74(CO); 153.83, 141.31, 110.33, 106.31(Fu); 50.46(C_2);
Ph	1d	90-92(98-99[51])	7.99-7.43(Ph); 4.47(α-H)	207.60(CO); 196.29(CO); 136.38, 133.65, 128.91, 128.70(Ph); 63.59(C_2);
	1j	101-103	7.98-7.43(Ph); 4.48(α-H)	207.47(CO); 196.17(CO); 136.30, 133.57, 128.83, 128.61(Ph); 63.48(C_2);
4-Pyridyl	1e	106-108	8.81; 7.74(Py); 4.42(α-H)	206.86(CO); 196.03(CO); 151.29, 142.00, 121.41(Py); 63.94(C_2);
	1k	98-100	8.80; 7.73(Py); 4.41(α-H)	206.82(CO); 196.04(CO); 151.29, 142.07, 121.41(Py), 63.94(C_2);
2-Furfuryl	1f	100-102	7.60; 7.25; 6.53(Fu); 4.30(α-H)	206.82(CO); 184.68(CO); 151.95, 147.17, 118.76, 112.61(Fu); 62.76(C_2);
	1l	104-106	7.61; 7.27; 6.55(Fu); 4.31(α-H)	206.75(CO); 184.62(CO); 151.90, 147.17, 118.71, 112.58(Fu); 62.68(C_2);



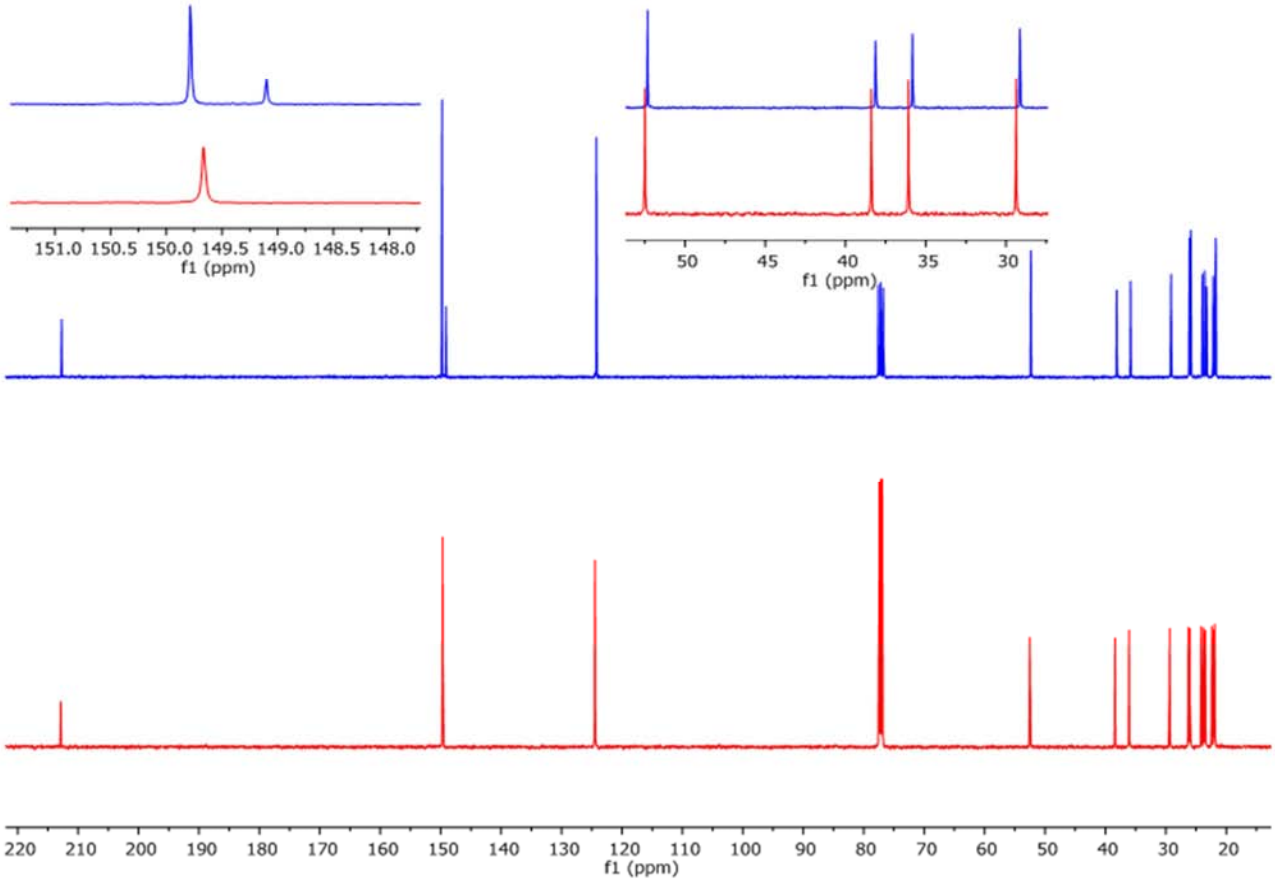


Figure 8. *The ^{1}H, ^{13}C NMR comparison of α-corner-syn and α-corner-anti isomers 1b (blue) and 1h (red).*

3. Conclusion

The paired configurational *cis*- and *trans*- (α-corner-*syn* and α-corner-*anti*) isomers were first observed and synthesized in the α-corner-monosubstituted cyclododecanone derivatives, their structures were characterized by ^{1}H, ^{13}C NMR, HR-ESI-MS spectral data and X-ray diffraction analysis. This kind of isomerism was first time postulated and confirmed in the [3333]-2-one conformation of α-monosubstituted cyclododecanone derivatives and could be extended to the other α-monosubstituted macrocyclic ketones.

4. Experimental (Optional)

General Information

All reactions were performed with magnetic stirring. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Organic solutions were concentrated under reduced pressure using a rotary evaporator. Melting points were measured on a Yanagimoto apparatus (Yanagimoto MFG Co., Kyoto, Japan) and are uncorrected. ^{1}H NMR spectra were obtained on Bruker DPX 300 spectrometer (Bruker Biospin Co., Stuttgart, Germany) with $CDCl_3$ as a solvent and TMS as an internal standard. High resolution mass spectral analysis was performed on a LTQ Orbitrap instrument (ThermoFisher scientific Inc., Waltham, USA). The Crystal structures were analyzed at Thermo Fisher ESCALAB 250 X-ray diffractometry.

Synthesis of *Cis*-α-corner-monosubstituted (α-corner-*syn*) cyclododecanones (1a-1f)

General procedure for *Cis*-α-monosubstituted (α-corner-syn) cyclododecanones 1a-1f: 1.20 g NaH (60%) (30 mmol, 3.0 eq) and 10 mL anhydrous toluene were added to 100 mL three-necked flask under the protection of nitrogen, stirred and added droplet (1.82 g, 10 mmol, 1.0 eq) anhydrous toluene solution at room temperature. Then stirred 5 h, and added (12 mmol, 1.2 eq) ethyl benzoate or benzyl chloride. After 12 h, stopped reaction, treated with HOAc, diluted with water, and extracted with ethyl acetate. Then the organic phase was washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed under the reduced pressure, the residue was chromatographed on silica gel and eluted with petroleum/ethyl acetate (100:1) to afford a white solid 1a and 1d. In a similar way, compounds 1b-1f were prepared.

Cis-α-corner benzylcyclododecanone (1a), a white solid, m.p. 68-70°C, yield 88%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.22-7.06 (m, 5H, ArH), 2.89-2.80 (m, 2H, $COCH_2$), 2.61-2.38 (m, 2H, $PhCH_2$), 2.22-2.12 (m, 1H, CH), 1.65-1.19 (m, 18H, 9xCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 214.1, 139.7, 128.6, 128.2, 125.9, 53.1, 38.2, 29.1, 25.9, 25.5, 23.9, 23.7, 23.6, 22.3, 22.0, 21.7; HRMS (ESI) m/z: calcd for $C_{19}H_{29}O$

$[M+H]^+$: 273.2213; found: 273.2210. The m.p., ^1H, ^{13}C NMR data were identical with those in the previous report [32].

Cis-α-corner (pyridin-4-ylmethyl)cyclododecanone (1b), m.p. 80-82°C, yield 83%; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.45-8.42 (m, 2H, PyH), 7.06-7.03 (m, 2H, PyH), 2.94-2.90 (m, 2H, $COCH_2$), 2.61-2.55 (m, 2H, $PyCH_2$), 2.20-2.11 (m, 1H, CH), 1.79-1.20 (m, 18H, $9xCH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.2, 149.5, 148.8, 124.0, 52.1, 37.9, 35.6, 28.9, 25.8, 25.6, 23.7, 23.3, 23.0, 21.9, 21.6, 21.5; HRMS (ESI) m/z: calcd for $C_{18}H_{28}NO$ [M+H]+: 274.2165; found: 274.2160.

Cis-α-corner (furan-2-ylmethyl)cyclododecanone (1c), m.p. 43-45°C, yield 87%; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.29-7.27 (m, 1H, FuH), 6.26-6.24 (m, 1H, FuH), 6.00-5.98 (m, 1H, FuH), 2.97-2.80 (m, 2H, $COCH_2$), 2.64-2.14 (m, 3H, $FuCH_2$+CH), 1.59-1.18 (m, 18H, $9xCH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.3, 153.4, 140.9, 109.9, 105.9, 50.1, 37.7, 29.1, 28.9, 25.8, 25.5, 23.8, 23.6, 23.3, 22.0, 21.8, 21.6; HRMS (ESI) m/z: calcd for $C_{17}H_{27}O_2$ $[M+H]^+$: 263.2006; found: 263.2003.

Cis-α-corner benzoylcyclododecanone (1d), m.p. 90-92°*C*, yield 86%; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.00-7.43 (m, 5H, ArH), 4.47 (dd, J = 11.7, 3.0 Hz, 1H, CH), 3.01-2.91 (m, 1H, $1/2xCH_2$), 2.34-2.29 (m, 1H, $1/2xCH_2$), 2.00-1.20 (m, 18H, $9xCH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.3, 196.0, 136.1, 133.4, 128.6, 128.4, 63.3, 36.2, 27.0, 25.9, 25.7, 23.8, 23.2, 22.8, 22.7, 22.2, 21.5; HRMS (ESI) m/z: calcd for $C_{19}H_{27}O_2$ $[M+H]^+$: 287.2006; found: 287.2009; $C_{19}H_{26}O_2Na$ $[M+Na]^+$: 309.1825; found: 309.1829. The m.p., ^1H, ^{13}C NMR data were identical with those in the previous report [38, 50].

Cis-α-corner (isonicotinoyl)cyclododecanone (1e), m.p. 106-108°*C*, yield 76%; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.82-8.80 (m, 2H, PyH), 7.75-7.73 (m, 2H, PyH), 4.43 (dd, J = 11.4, 3.0 Hz, 1H, CH), 2.99-2.89 (m, 1H, $1/2xCH_2$), 2.34-2.28 (m, 1H, $1/2xCH_2$), 2.02-1.25 (m, 18H, $9xCH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.7, 195.9, 151.1, 141.9, 121.2, 63.7, 36.6, 26.9, 26.0, 25.7, 23.9, 23.3, 22.8, 22.7, 22.2, 21.6; HRMS (ESI) m/z: calcd for $C_{18}H_{26}NO_2$ $[M+H]^+$: 288.1958; found: 288.1961.

Cis-α-corner (furan-2-carbonyl)cyclododecanone (1f), m.p. 100-102°*C*, yield 87%; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.60 (dd, J = 1.8, 0.8 Hz, 1H, FuH), 7.25 (dd, J = 3.6, 0.8 Hz, 1H, FuH), 6.54 (dd, J = 3.6, 1.8 Hz, 1H, FuH), 4.30 (dd, J = 11.5, 3.1 Hz, 1H, CH), 2.96-2.84 (m, 1H, $1/2xCH_2$), 2.31-2.27 (m, 1H, $1/2xCH_2$), 2.20-1.25 (m, 18H, $9xCH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.6, 184.4, 151.7, 146.9, 118.5, 112.4, 62.5, 37.1, 26.6, 25.7, 25.4, 23.9, 23.4, 23.1, 22.8, 22.2, 21.7; HRMS (ESI) m/z: calcd for $C_{17}H_{25}O_3$ $[M+H]^+$: 277.1798; found: 277.1802; $C_{17}H_{24}O_3Na$ $[M+Na]^+$: 299.1618; found: 299.1624.

Synthesis of *Trans*-α-corner monosubstituted (α-corner-*anti*) cyclododecanones (1g-1l)

Synthesis of intermediates α-corner *anti*-substituted hydroxylmethyl cyclododecanones: cyclododecanone 5.46 g (30 mmol, 1.0 eq), 30 mL methanol, and 3.1 mL benzaldehyde (30 mmol, 1.0 eq) were added into a 150 mL flask, stirred and dropped 45 mL 0.01M NaOH solution at room temperature. After 10 h, stopped the reaction, and the solution was extracted with ethyl acetate. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. Then the solvent was removed under reduced pressure, the residue was chromatographed on silica gel and eluted with petroleum/ethyl acetate (50:1) to give a white solid 2a. In a similar way, 2b and 2c were prepared.

α-Corner *anti*-2-(hydroxy(phenyl)methyl)cyclododecanone (2a), m.p. 110-112°C (107-109°C [40]), yield 85%. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.36-7.31 (m, 5H, ArH), 4.81 (d, J = 9.3 Hz, 1H, CHO), 3.00-2.92 (m, 1H, CH), 2.81-2.70 (m, 1H, CH), 2.58 (brs, 1H, OH), 2.50-2.40 (m, 1H, CH), 1.83-1.19 (m, 18H, $9xCH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 214.8, 142.1, 128.5, 127.9, 126.6, 75.5, 59.0, 39.5, 27.3, 26.3, 25.9, 24.2, 23.8, 23.7, 22.7, 22.3, 21.5; HRMS (ESI) m/z: calcd for $C_{19}H_{28}NaO_2$ $[M+Na]^+$: 311.1982; found: 311.1983. The m.p., ^1H, ^{13}C NMR data were identical with those in the previous report [41].

α-Corner *anti*-2-(hydroxy(4-pyridyl)methyl)cyclododecanone (2b), m.p. 90-92°C, yield 75%. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.58-8.55 (m, 2H, PyH), 7.28-7.25 (m, 2H, PyH), 4.84 (d, J = 8.1 Hz, 1H, CHO), 3.27 (brs, 1H, OH), 2.98-2.91 (m, 1H, CH), 2.83-2.72 (m, 1H, CH), 2.36-2.28 (m, 1H, CH), 1.91-1.20 (m, 18H, $9xCH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 214.4, 151.7, 149.5, 121.7, 73.8, 58.3, 39.9, 27.3, 26.3, 25.8, 24.9, 24.0, 23.8, 22.8, 21.7; HRMS (ESI) m/z: calcd for $C_{18}H_{28}NO_2$ $[M+H]^+$: 290.2115; found: 290.2118.

α-Corner *anti*-2-(hydroxy(2-furfuryl)methyl)cyclododecan- one (2c), m.p. 114-116°C, yield 90%. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.39 (dd, J = 1.8, 0.8 Hz, 1H, FuH), 6.34 (dd, J = 1.8, 3.5 Hz, 1H, FuH), 6.29 (dd, J = 3.5, 0.8 Hz, 1H, FuH), 4.90 (dd, J = 9.0, 5.1 Hz, 1H, CHO), 3.24-3.17 (m, 1H, CH), 2.86-2.76 (m, 1H, CH), 2.68 (d, J = 5.1 Hz, 1H, OH), 2.46-2.36 (m, 1H, CH), 1.87-1.21 (m, 18H, $9xCH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 214.4, 154.4, 142.2, 110.2, 107.4, 68.3, 56.2, 39.3, 27.1, 26.3, 25.9, 24.2, 23.7, 23.5, 22.5, 22.4, 21.5; HRMS (ESI) m/z: calcd for $C_{17}H_{26}NaO_3$ $[M+Na]^+$: 301.1774; found: 301.1772.

Synthesis of intermediates α-corner *anti*-substituted acyloxymethyl cyclododecanones: 576 mg 2a (2.0 mmol, 1.0 eq), 488 mg DMAP (4.0 mmol, 2.0 eq) and 8.0 mL CH_2Cl_2 were added to a 50 mL three-necked flask under nitrogen, stirred 1 h at ambient temperature. Then 0.54 mL (4.0 mmol, 2.0 eq) O-phenyl carbonochloridothioate was added and reacted 18 h. Extracted with CH_2Cl_2, the organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in vaccoum, the residue was chromatographed on silica gel and eluted with petroleum/ethyl acetate (30:1) to produce a yellow solid α-corner *anti*-O-((2-oxocyclododecyl)(phenyl)methyl) O-phenyl carbonothioate (2aa). In a similar way, the esters 2ba and 2cb were prepared.

α-Corner *anti*-O-((2-oxocyclododecyl)(phenyl)methyl) O-phenyl carbonothioate (2aa), m.p. 118-120°*C*, yield 79%; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.44-7.25 (m, 8H, ArH), 7.01-6.98 (m, 2H, ArH), 6.37 (d, 1H, J = 9.6 Hz), 3.33-3.26 (m,

1H, CH), 2.80-2.57 (m, 2H, CH_2), 1.92-1.70 (m, 2H, CH_2), 1.33-1.20 (m, 16H, 8xCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.7, 192.9, 152.9, 136.2, 129.0, 128.5, 128.2, 127.8, 126.0, 121.5, 85.3, 56.8, 38.0, 25.9, 25.9, 25.8, 23.6, 23.1, 22.8, 23.6, 23.1, 22.8, 21.9, 21.6, 21.3; HRMS (ESI): m/z calcd for $C_{26}H_{33}SO_3$ $[M+H]^+$: 425.2144; found: 424.2132.

α-Corner *anti*-O-((2-oxocyclododecyl)(4-pyridyl)methyl) O-phenyl carbonothioate (2ba), m.p. 110-112°*C*, yield 72%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.67 (d, 2H, J = 6.0 Hz, ArH), 7.38-7.27 (m, 5H, ArH), 7.02-6.99 (m, 2H, ArH), 6.32 (d, 1H, J = 10.5 Hz), 3.30-3.22 (m, 1H, CH), 2.83-2.52 (m, 2H, CH_2), 1.97-1.93 (m, 1H, CHH), 1.67-1.40 (m, 1H, CHH), 1.32-1.22 (m, 16H, 8xCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 209.3, 192.8, 152.8, 149.9, 145.0, 129.1, 126.2, 122.3, 121.4, 83.3, 55.9, 38.4, 25.8, 25.7, 23.6, 23.1, 22.8, 21.8, 21.5, 21.3; HRMS (ESI): m/z calcd for $C_{25}H_{32}NO_3S$ $[M+Na]^+$: 426.2097; found: 426.2080.

α-Corner *anti*-O-((2-Oxocyclododecyl)(2-furfuryl) methyl)-1H-imidazole-1-carbothioate (2ca), m.p. 148-150°*C*, yield 56%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.13 (s, 1H, ArH), 7.40-7.37 (m, 2H, ArH), 7.05 (s, 1H, ArH), 6.37-6.31 (m, 2H, ArH), 5.25 (d, 1H, J = 10.8 Hz, CHO), 3.47-3.40 (m, 1H, CH), 2.81-2.73 (m, 1H, CHH), 2.50-2.41 (m, 1H, CHH), 1.91-1.88 (m, 1H, CHH), 1.61-1.23 (m, 17H, 8xCH_2+CHH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 209.6, 164.2, 150.8, 142.3, 135.0, 130.5, 115.5, 110.2, 108.6, 53.3, 42.5, 37.9, 27.6, 25.8, 25.7, 23.5, 22.8, 22.4, 21.9, 21.2, 21.1; HRMS (ESI): m/z calcd for $C_{24}H_{31}SO_4$ $[M+H]^+$: 415.1937; found: 415.1926.

α-Corner *anti*-(5-phenoxycarbonylfuran-2-ylmethyl)cyclododecanone (2cc), m.p. 66-68°*C*, yield 76%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37-7.14 (m, 5H, ArH), 6.71 (s, 1H, ArH), 3.08-2.94 (m, 2H, CH_2), 2.74-2.69 (m, 2H, CH_2), 1.67-1.64 (m, 1H, CHH), 1.31-1.20 (m, 18H, 9xCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.2, 167.0, 159.6, 151.4, 135.5, 129.6, 126.4, 122.8, 121.1, 109.3, 50.0, 38.4, 29.6, 29.1, 26.1, 25.9, 24.2, 23.8, 23.6, 22.4, 21.9; HRMS (ESI): m/z calcd for $C_{25}H_{35}O_5$ $[M+CH_3OH+H]^+$: 415.2484; found: 415.2486.

Reduction of the ester intermediate 2aa: 0.24 mL tributylstannane (0.8 mmol, 4 eq) and 15 mL toluene were added into a 50 mL three-necked flask under nitrogen, heated to reflux. 84 mg 2aa (0.2 mmol, 1 eq) and 33 mg AIBN (0.2 mmol, 1 eq) solution in 8 mL toluene were gradually dropped into above reaction system. Reacted 3 h and cooled to room temperature, removed the solvent. The sample was chromatographed on silica gel and eluted with petroleum/ethyl acetate (50:1) to afford a white solid 1g. In similar way, 1h and 1i were prepared with compounds 2ba and 2cb as the raw materials.

Trans-α-corner benzylcyclododecanone (1g), m.p. 55-57°*C*, yield 76%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30-7.14 (m, 5H, ArH), 2.97-2.88 (m, 2H, CH_2), 2.68-2.46 (m, 2H, CH_2), 2.30-2.20 (m, 1H, CH), 1.75-1.58 (m, 4H, 2xCH_2), 1.35-1.22 (m, 14H, 7xCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 214.3, 140.0, 128.9, 128.5, 126.3, 53.4, 38.7, 37.7, 29.6, 26.3, 25.9, 24.3, 24.2, 24.0, 22.8, 22.5, 22.1; HRMS (ESI) m/z: calcd for $C_{19}H_{29}O$ $[M+H]^+$: 273.2213; found: 273.2203.

Trans-α-corner 4-pyridylmethylcyclododecanone (1h), m.p. 73-75°*C*, yield 81%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.48-8.46 (m, 2H, PyH), 7.09-7.07 (m, 2H, PyH), 2.97-2.93 (m, 2H, CH_2), 2.64-2.60 (m, 2H, CH_2), 2.20-2.14 (m, 1H, CH), 1.84-1.26 (m, 18H, 9xCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.9, 149.7, 149.6, 124.5, 52.5, 38.4, 36.1, 29.4, 26.2, 26.0, 24.1, 23.8, 23.5, 22.4, 22.0, 21.9; HRMS (ESI) m/z: calcd for $C_{18}H_{28}NO$ [M+H]+: 274.2165; found: 274.2253.

Trans-α-corner 2-furfurylmethylcyclododecanone (1i), m.p. 35-37°*C*, yield 65%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33 (dd, J = 1.8, 0.8 Hz, 1H, FuH), 6.29 (dd, J = 3.5, 1.8 Hz, 1H, FuH), 6.03 (dd, J = 3.5, 0.8 Hz, 1H, FuH), 3.00-2.76 (m, 2H, CH_2), 2.71-2.26 (m, 3H, CH_2+CH), 1.71-1.29 (m, 18H, 9xCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.7, 153.8, 141.3, 110.3, 106.3, 50.4, 38.1, 29.6, 29.4, 26.2, 25.9, 24.2, 24.0, 22.4, 22.2, 22.0, 21.6; HRMS (ESI) m/z: calcd for $C_{17}H_{27}O_2$ $[M+H]^+$: 263.2006; found: 263.1998.

Oxidation of intermediate 2a: 3.11 g PCC (14.4 mmol, 3.0 eq), 2.0 g celite and 20 mL CH_2Cl_2 were added into a 100 mL flask, stirred and added 1.38 g 2a (4.8 mmol, 1.0 eq) solution in 20 mL CH_2Cl_2 at ambient temperature. After 4 h, stopped the reaction, removed the solvent, the residue was chromatographed on silica gel and eluted with petroleum/ethyl acetate (30:1) to produce a white solid 1j. In similar procedure, 1k and 1l were prepared with compounds 2b and 2c.

Trans-α-corner benzoylcyclododecanone (1j), m.p. 101-103°*C*, yield 91%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00-7.43 (m, 5H, ArH), 4.48 (dd, J = 11.7, 2.9 Hz, 1H, CH), 2.98-2.91 (m, 1H, 1/2xCH_2), 2.34-2.29 (m, 1H, 1/2xCH_2), 2.00-1.24 (m, 18H, 9xCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.4, 196.2, 136.3, 133.5, 128.8, 128.6, 63.4, 36.3, 27.2, 26.1, 25.8, 24.0, 23.4, 23.0, 22.9, 22.3, 21.7; HRMS (ESI) m/z: calcd for calcd for $C_{19}H_{27}O_2$ $[M+H]^+$: 287.2006; found: 287.2008; $C_{19}H_{26}NaO_2$ $[M+Na]^+$: 309.1825; found: 309.1829.

Trans-α-corner isonicotinoylcyclododecanone (1k), m.p. 98-100°*C*, yield 68%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.82-8.79 (m, 2H, PyH), 7.74-7.72 (m, 2H, PyH), 4.42 (dd, J = 11.4, 3.0 Hz, 1H, CH), 2.99-2.88 (m, 1H, 1/2xCH_2), 2.32-2.27 (m, 1H, 1/2xCH_2), 2.01-1.24 (m, 18H, 9xCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.8, 196.0, 151.2, 142.0, 121.4, 63.9, 36.8, 27.1, 26.1, 25.9, 24.0, 23.4, 23.0, 22.9, 22.4, 21.8; HRMS (ESI) m/z: calcd for $C_{18}H_{26}NO_2$ $[M+H]^+$: 288.1958; found: 288.1960.

Trans-α-corner furan-2-carbonylcyclododecanone (1l), m.p. 104-106°*C*, yield 72%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.61 (d, J = 1.6 Hz, 1H, FuH), 7.27 (d, J = 3.6 Hz, 1H, FuH), 6.54 (dd, J = 3.6, 1.6 Hz, 1H, FuH), 4.32 (dd, J = 11.5, 3.1 Hz, 1H, CH), 2.96-2.85 (m, 1H, 1/2xCH_2), 2.32-2.30 (m, 1H, 1/2xCH_2), 2.27-1.27 (m, 18H, 9xCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.7, 184.6, 151.8, 147.2, 118.7, 112.5, 62.6, 37.2, 26.8, 25.8, 25.6, 24.0, 23.6, 23.3, 23.0, 22.4, 21.8; HRMS (ESI) m/z: calcd for $C_{17}H_{25}O_3$ $[M+H]^+$: 277.1798; found: 277.1798; $C_{17}H_{24}O_3Na$ $[M+Na]^+$: 299.1618; found: 299.1616.

X-ray diffraction analysis of Compounds 1a, 1h, 1k and 2c.

The good colorless crystals of compounds 1a, 1h, 1k and 2c were obtained from their n-hexane, or n-hexane/$CHCl_3$ or n-hexane/CH_2Cl_2 or ethanol solutions. Their structure

parameters were shown in supporting information. The crystallographic data of compounds 1a, 1h, 1k and 2c in this paper have been deposited with the Cambridge Crystallographic Data Centre with the accession number-CCDC 1904027-1904030. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk /data_request/cif.

Supporting Information

The ^{1}H and ^{13}C NMR of title compounds, crystal structures and their parameters of compounds 1a-2c.

Supporting Information File 1: Supporting Information-2021.

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