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Synthesis and Stereochemical Behavior of 1-Aryloctahydroisobenzofuro[7a,1-*d*]oxazole Ring System: New Examples of Isolable Rotamers.

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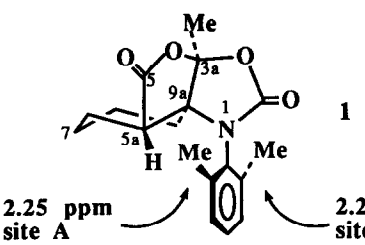
Abstract : Preparation and stereochemical behavior of new examples of isolable rotamers are described. Reaction of hydroxylactone **2** with isocyanates **3** - **11** gave the corresponding **12** - **20** in good yields. Among them, *ortho* di-substituted ones gave isolable rotamers. The behavior of *ortho* mono-substituted derivatives is also discussed.

Research on isolable rotamers has drawn much attention from chemists from the viewpoint of both molecular interactions and chemical reactivities.[2] Such rotamers can be isolated provided that the barrier to rotation about the bond in question is sufficiently high and that the system possesses an asymmetric element. In recent years, a number of rotamer pairs have been investigated in fluorenes,[3] triptycenes,[4] and aryldi-*t*-butylcarbinols.[5] In the course of our synthetic study toward biologically active heterocyclic systems, we have developed the base-catalyzed stereoselective one pot preparation of the title heterocyclic system.[6] In the report, we have described the preparation of a 2,6-dimethylphenyl derivative of tricyclic isobenzofuro[7a,1-*d*]oxazoledione **1**. The ^{1}H-NMR and NOE study of compound **1** revealed that the two aromatic methyl groups were magnetically non-equivalent (2.25 and 2.28 ppm), and the higher field signal was assigned to the methyl close to 5a-H. The result of *semi*-empirical MO calculation (MNDO-PM3)[7] for compound **1** also suggested that the dihedral angle between the oxazolidinone ring and the benzene ring was almost perpendicular in the stable conformation of **1**. This means there are two stable sites for the *ortho* substituents of the phenyl group, *i.e.*, the foreside of the oxazolidinone ring (site A) and the back side of it (site B) as shown in Scheme 1. Therefore, if one of the aromatic methyl groups is substituted, such rotamers will be expected to be obtained. This assumption was realized, and we report here a new ring system that gives isolable rotamers at room temperature due to the restricted rotation about the N-C single bond.



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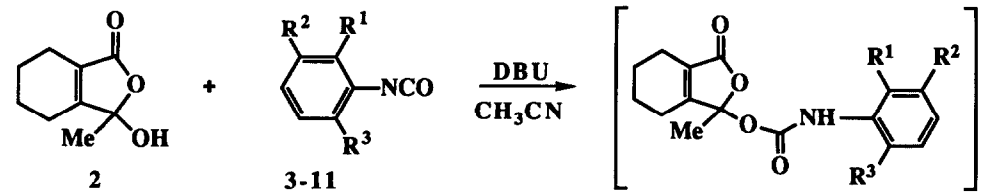
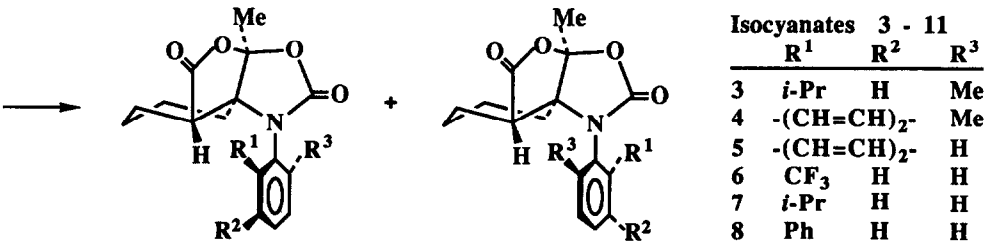
Scheme 1

For the isolation of the rotamers at room temperature, it should be noted that a free energy of activation higher than *ca.* 23 kcal/mol is required.[2] Since compound **1** has a highly rigid, unique tricyclic framework, the choice of *ortho* substituents that produce high enough rotation barriers without raising the ground state energy is

very important. Therefore, not only the bulkiness but also the shape of the *ortho* substituents would play an important role. Based on such a viewpoint, we planned to prepare several *ortho* di- and mono-substituted derivatives. To our surprise, the reaction of hydroxylactone **2** and isocyanates **3-11** proceeded quite well even in the case of highly crowded isocyanates in the presence of a catalytic amount of 1,8-diazabicyclo[5.4.0]-undecene (DBU) at room temperature as shown in Scheme 2. All the isobenzofuro[7a,1-*d*]oxazolediones **12-20** prepared were characterized by NMR (involving NOE, COSY, CH-COSY measurements), IR, MS, and elemental analysis. The results are summarized in Table 1, together with their data for interconversions.



2 **3-11**



12a-20a **12b-20b**

Scheme 2

Isocyanates 3 - 11

	R^1	R^2	R^3
3	*i*-Pr	H	Me
4	-(CH=CH)$_2$-		Me
5	-(CH=CH)$_2$-		H
6	CF_3	H	H
7	*i*-Pr	H	H
8	Ph	H	H
9	Me	H	H
10	OMe	H	H
11	F	H	H

Table 1. Preparation of Tricyclic Oxazolidinones **12 - 20** and their kinetic data for interconversions.

Compound	R^1	R^2	R^3	Reaction Time (h)	Yield (%)	m.p. (°C)	Equilibrium ratio a/b[a]	Data for interconversions
12a	*i*-Pr	H	Me	48	56	240-2		$\Delta G^{\ddagger}$ = 45-6 kcal/mol(270°C, **a** → **b**).
12b	*i*-Pr	H	Me		24	228-30		$\Delta G^{\ddagger}$ = 44 kcal/mol(270°C, **b** → **a**).
13a	-(CH=CH)$_2$-		Me	2	73	258-60		$\Delta G^{\ddagger}$ > 35 kcal/mol.
14	-(CH=CH)$_2$-		H	24	73	209-10	1.0	*Tc*>150°C, signal broadening at 150°C.[c]
15	CF_3	H	H	48	43	215-6	0.43	$\Delta G^{\ddagger}$ = 21.3 kcal/mol(0°C, **a** → **b**).
16	*i*-Pr	H	H	24	70	180-2	0.88	*Tc*>150°C, signal broadening at 150°C.[c]
17	Ph	H	H	24	69	236-7	0.83	*Tc*>100°C, decompose at 150°C.[c]
18	Me	H	H	2	78	233-5	0.92	*Tc*>100°C[c], $\Delta G^{\ddagger}$ = 18.8 kcal/mol(23°C, **a** → **b**). $\Delta G^{\ddagger}$ = 19.0 kcal/mol(23°C, **b** → **a**).
19	OMe	H	H	24	80	203-5	0.18[b]	*Tc*=0°C[d], $\Delta G^{\ddagger}$ = 13.0 kcal/mol.
20	F	H	H	1	73	235-6		*Tc*<-60°C.[d]

a) Determined in $CDCl_3$ at room temperature. b) Determined in $CDCl_3$ at -60°C c) Measured in DMSO-d_6. d) Measured in $CDCl_3$.

The reaction of hydroxylactone **2** and isocyanate **3** yielded two isomeric compounds in the ratio of 70:30 in 80 % (total) yield. These compounds were easily separated by recrystallization and column chromatography. The NMR and IR spectra of these compounds were very similar to each other, but the major product **12a** had a higher melting point, and was less soluble in ether and less mobile on TLC than the minor product **12b**.[8] The conformation was elucidated by NOE measurements. The NOE study of **12a** clarified that 5a-H (2.62, dd) is close to CH (2.81, septet) in the isopropyl group and the aromatic Me (2.29, s) is close to 9-H_{ax} (1.70, m). On the other hand, the NOE study of **12b** revealed that the aromatic Me(2.26, s) is close to 5a-H(2.71, dd), and the CH(2.91, septet) of the isopropyl group is close to 9-H_{ax}(1.70) and 9-H_{eq}(2.20). In both molecules, the diastereotopic methyl signals of the isopropyl groups had different chemical shifts in both ^{1}H- and ^{13}C-NMR. The assignment of these signals was achieved by considering the combination of NOE, HH-, and CH-COSY measurements. In both rotamers, one of the methyl groups close to the cyclohexane ring appeared downfield in ^{1}H and upfield in ^{13}C-NMR (see Table 2). In highly crowded systems where severe steric interactions are unavoidable, such upfield shifts in ^{13}C-NMR have been reported in terms of steric compression effects.[9,10] These facts clearly indicate these are the rotamers due to the restricted rotation about the N-C bond.

We proved this consideration to be true by observing the isomerization of each pure isomer separately. When **12a** was heated at 270°C for 8h in dihydroanthracene, about 10% of isomerization to **12b** was observed by NMR of the crude reaction mixture. Similarly, compound **12b** was isomerized to **12a** (12%) on heating at 270°C for 2h. The products were separated by column chromatography and identified by m.p., IR, and NMR comparison. At 280°C in dihydroanthracene, however, both rotamers decomposed within a few hours. Although we could not determine the equilibrium ratio of these rotamers due to the partial sublimation and decomposition at high temperature, the barrier to interconversion was roughly estimated to be $\Delta G^{\ddagger}$ = 45-6 kcal/mol (270°C) for the **12a** to **12b** process and to be $\Delta G^{\ddagger} \approx$ 44kcal/mol(270°C) for the **12b** to **12a** process.

The reaction of the hydroxylactone **2** and isocyanate **4** also gave such a rotamer. In this case, however, only one rotamer **13a** was obtained in high yield and none of **13b** was found in the crude reaction mixture. The stereochemical structure of **13a** was also determined by NOE measurements. The attempt to obtain the isomeric **13b** by the thermal isomerization of **13a** was unsuccessful, because **13a** decomposed with effervescence on heating at 250°C in dihydroanthracene within 15 min. The rotational barrier of this compound was considered higher than 35kcal/mol, because this compound did not show any interconversion on heating(200°C) for 1h in diphenyl ether and was recovered unchanged. Since the rotational barrier of this class of compounds is so high, the rotamer ratio in the cyclization reaction can be assumed to be the result of kinetic control. The population of rotamers will reflect the interactions between the bicyclic moiety and the *ortho* di-substituents of the benzene ring in the cyclization step. The reason for the siteselectivity in this system should be studied further.

We next prepared *ortho* mono-substituted derivatives **14** - **20** in order to lower the energy barrier to rotation. Among them, we found that each of the compounds **14** - **18** consisted of a mixture of rotamer pair, but they were inseparable due to fast interconversion at room temperature. The estimated barriers to interconversion of these compounds increase roughly in the following order; **18<17<16,15<14** (≤23kcal/mol)[2].

Figure 1 shows the ^{1}H-NMR and NOE of **18** in $CDCl_3$ solution at 23°C, together with the kinetic data for interconversion obtained by the saturation transfer method.[11] In this Figure, irradiation at 3.05 ppm (5a-H) enhanced 7.04 ppm (6'-H), accompanied by saturation transfer from 3.05 ppm to 2.50 ppm. On the contrary, irradiation at 2.50 ppm did not enhance the aromatic signal; only saturation transfer to 3.05 ppm was observed. We examined the NOE enhancement for every possible combination of pairs of signals and found the saturation

The rate constants k of rotation between the rotamers **18a** and **18b** obtained by the saturation transfer method at 23°C.

T_{1Aeff} (s)	1.65	T_{1Beff} (s)	1.51
$MA / M0A$	0.86	$MB / M0B$	0.91
k_A (s^{-1})	0.08	k_B (s^{-1})	0.06

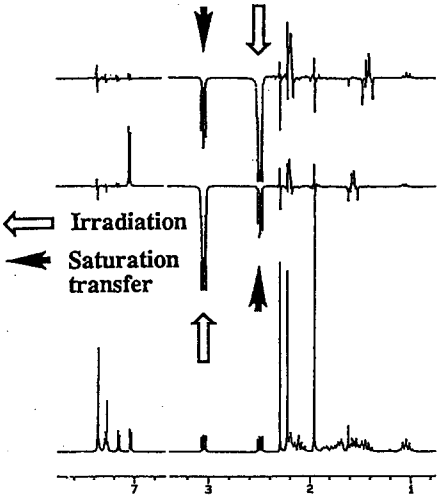


Fig.1 ^{1}H-NMR Spectra of Compound **18.**

transfer from the irradiation signal to the corresponding signal in the other rotamer in all cases. When the temperature was lowered to -50°C in $CDCl_3$, the signal of the cyclohexane region was sharpened, but the ratio of the two isomers was practically unchanged. All these facts support the slow site exchange between **18a** and **18b**. Thus these rotamers are inseparable at room temperature. The rate constants of interconversion between **18a** and **18b** were determined by the saturation transfer method. From these data, we estimated the barrier to conversion of **18a** to **18b** to be $\Delta G^{\ddagger}$ = 18.8 kcal/mol and that to the reverse process to be $\Delta G^{\ddagger}$ = 19.0 kcal/mol at 23°C. Measurement of the ^{1}H spectrum at 100°C in DMSO-d_6 showed that the shift difference in aromatic methyl signals (0.13 ppm at 25°C) narrowed to 0.11 ppm accompanied by line broadening. At a higher temperature in DMSO-d_6, unfortunately compound **18** rapidly decomposed into the carbamate due to *retro*-Michael addition, therefore determination of the coalescence temperature was unsuccessful.

In compound **17**, nearly a 1:1 ratio of rotamers was observed. A large chemical shift difference due to the magnetic anisotropy of the benzene ring was detected in the ^{1}H spectra of these rotamers, *i.e.*, one of the chemical shifts of 3a-Me, assignable to rotamer **17b**, appeared at 1.47ppm (3a-Me of **17a** 1.83ppm) and 5a-H of rotamer **17a** at 2.15ppm (5a-H of **17b** 2.93ppm). The barrier to interconversion of these rotamers was considered slightly higher than that of **18**, because we did observe a small saturation transfer in NOE measurement at room temperature.

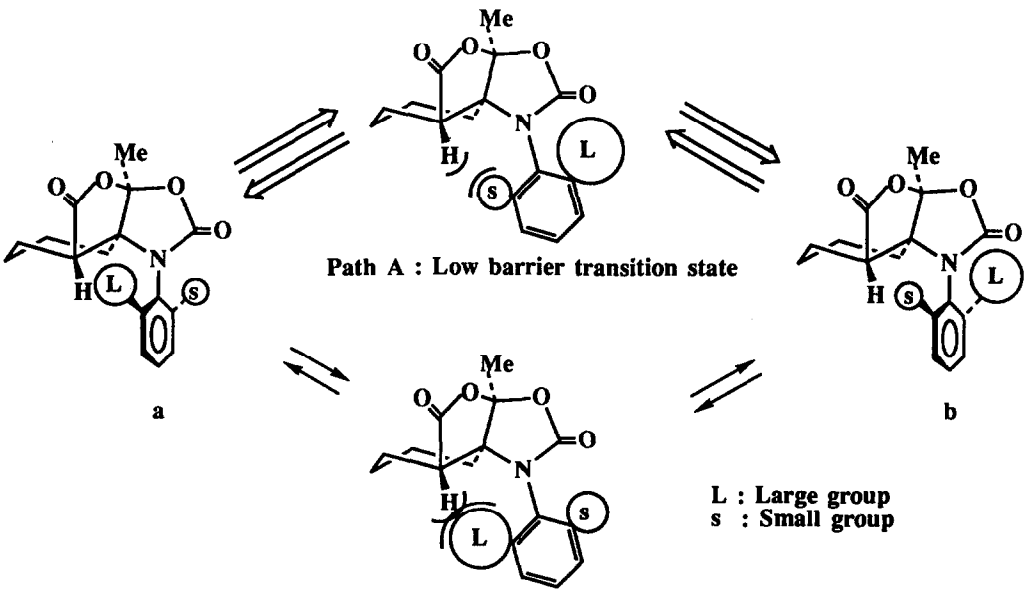
The rotational behavior of compound **15** is rather interesting. When the 90MHz ^{1}H-NMR of compound **15** was taken without delay after the preparation of the $CDCl_3$ solution of **15** (about 2 min. required), the chart exhibited the rotamer ratio to be **a**:**b**=7:3. However, the ratio gradually changed and settled at equilibrium, **a**:**b**=3:7, after 1h. A similar phenomenon was again observed by NMR when the solid recovered from the solution which had attained equilibrium was dissolved in $CDCl_3$. This fact apparently suggests that the stable conformation of **15** in solution is different from the solid state structure. Actually, when compound **15** was dissolved in $CDCl_3$ at 0°C and immediately submitted to ^{1}H-NMR measurement at the same temperature, the rotamer ratio was found to be **15a**:**15b**=95:5(after 13min. of sample preparation). Therefore, we could

fortunately estimate the energy barrier to isomerization from **15a** to **15b** by measuring the isomerization rate at 0°C and obtained the value $\Delta G^{\ddagger}$ = 21.3kcal/mol (k_A / k_B=2.23, k_A=5.0x10^{-5} s^{-1} at 0°C, assuming a reversible first-order process).

The ^{1}H-NMR spectra of compounds **16** and **14** showed the presence of nearly 1:1 rotamers. The barriers to interconversion of these compounds were considered nearly equal to that of **15** or higher, because we did not detect saturation transfer in the NOE measurements at room temperature. Their TLC (silica gel, *n*-hexane-AcOEt 9:1 as an eluent) exhibited two indistinct spots. The HPLC chart of these compounds showed a very broad, plateau-like peak. This will indicate that the slow interconversion between the rotamers occurs in the HPLC column. Therefore, we could not separate the rotamers.

In the case of the smaller *ortho* mono-substituent, the benzene ring rotates faster than the NMR time scale at room temperature. Compounds **19** and **20** belong to the class possessing a rather low energy barrier to rotation about the N-C bond. Compound **19** showed distinct temperature-dependent behavior. At 25°C the 400 MHz ^{1}H-NMR spectrum showed broad signals of OMe and 5a-H. In 100 MHz ^{13}C-NMR, the signals assignable to C-5a, C-9, C-9a, and OMe were very broad and split into a multiplet due to slow rotation of the benzene ring. At low temperature (-60°C), the OMe and 5a-H signals decoalesced into two sets, indicating a 15:85 mixture of rotamers **19a** and **19b**. For the estimation of the rotation energy barrier for compound **19**, we carried out dynamic NMR spectroscopy. The OMe signal of compound **19** coalesced at about 0°C (400 MHz), and the barrier to rotation was estimated to be $\Delta G^{\ddagger}$ = 13.0 kcal/mol at 0°C by the measurement of ^{1}H-NMR from -50°C to 20°C and computer simulation of the total line-shape method.[12] The barrier to rotation of compound **20** was very low, because the coalescence temperature was below -60°C.

Finally, we discuss the mechanism of the interconversion of this ring system. For the rotation of the benzene ring, two possible pathways are considered as illustrated in Scheme 3.



Scheme 3

Path A is the course in which the bulkier group passes through the side of the carbonyl group and path B is the course in which the bulkier group passes through the cyclohexane ring side. Since this skeleton has no symmetric element, the energy barriers of paths A and B should be different. From the CPK molecular model study, we speculate that the energetically favored pathway for interconversion would be path A, because in path B, steric repulsion between the cyclohexane ring and the large *ortho* substituent might be sufficient to prevent the exchange of sites. Therefore, we believe the main course of interconversion between the rotamers should be attributable to the tumbling of the bulkier group under the carbon-oxygen double bond.

At a glance, the order of the barrier to tumbling roughly parallels the generally accepted order of the size of the *ortho* substituent that interacts with the carbonyl oxygen. However, we must point out at least that the barrier is also affected by the conformational flexibility of the *ortho* substituent. For example, we prepared compound **14** in order to fix the conformation of one of the hydrogens of the methyl group in compound **18** without changing its bulkiness. Comparing the barriers of these compounds, we recognize that such conformation locking actually raises the barrier by several kilocalories. This observation can be explained as follows. At the transition state of tumbling, the methyl group in compound **18** can avoid severe steric interaction with the carbonyl oxygen by several motions, for example, bending the C_{arom}-CH_3 bond or a gear-like rotation of the methyl group. In compound **14**, however, such flexible motion is extremely restricted.

Thus we have outlined the new isolable rotamer pairs produced in a roof-shaped template of tricyclic oxazolidinones. The stereochemical behavior of rotation in this system was found to vary according to the bulkiness and the shape of the *ortho* substituents. The highly functionalized rigid structure of this framework would provide us with new knowledge of stereochemistry and a new approach to a stereoselective construction of molecules.

EXPERIMENTAL

Melting points were determined by a hot stage apparatus, and were not corrected. IR spectra were recorded on a SHIMADZU IR-440 spectrophotometer. NMR spectra were recorded on a Varian EM-390 spectrometer, a Varian Unity400, or a JEOL JNM-GSX400 spectrometer in $CDCl_3$ or DMSO-d_6 solutions with tetramethylsilane as an internal standard. Throughout this section chemical shifts (δ) are given in ppm and coupling constants (J) are given in Hz. Mass spectra were obtained on a HITACHI M-80 spectrometer using the electron impact (EI) or the chemical ionization (CI) method. Isocyanates **5-7** and **9 - 11** were commercially available and used without further purifications. Isocyanates **3**, **4**, and **8** were prepared with a slight modification of the literature,[13] and had the following boiling points and yields(based on the corresponding aniline). **3**: 65-66°C(2mmHg), 85%. **4**: 114-6°C(3mmHg), 88%. **8**: 112-3°C(3mmHg), 83%.

General procedure for tricyclic oxazolidinones 12 - 20: To a stirred solution of hydroxylactone **2** (0.84 g, 5 mmol) and an appropriate isocyanate **3 - 11** (5 mmol) in acetonitrile (10 ml, dried over molecular sieves 3A) was added DBU (40 mg, 0.25 mmol) at ambient temperature. The reaction was monitored by TLC or ^{1}H-NMR. After being stirred for 1 - 48 h, acetonitrile was evaporated under reduced pressure. A small amount of chloroform was added to the residue followed by gradual addition of ether to afford **12 - 20**.

Separation of rotamers 12a, 12b: Recrystallization according to the general procedure gave almost pure **12a**(0.49 g). The mother liquid was concentrated and chromatographed on silica gel (eluent; *n*-hexane:$CHCl_3$:AcOEt = 5:5:1) to give **12a**(0.47 g) and **12b**(0.41 g).

Tricyclic oxazolidinone 12a: Anal. Calcd for $C_{20}H_{25}NO_4$: C,69.95; H,7.34; N,4.08%. Found: C,69.64; H,7.21; N,4.22%. MS(CI) 344(M^++1, 100%); IR(KBr) 1780cm^{-1}; ^{1}H-NMR($CDCl_3$) 0.98(1H,m,7-H_{ax}), 1.03(3H,d,J=6.8, one of the CH$\underline{Me_2}$ remote from 5a-H), 1.35(3H,d,J=6.8, one of the CH$\underline{Me_2}$ close to 5a-H), 1.45(2H,m,6-H_{ax}, 8-H_{ax}), 1.70(3H,m,7-H_{eq}, 8-H_{eq}, 9-H_{ax}), 1.97(3H,s,3a-Me), 2.20(2H,m,6-H_{eq},9-H_{eq}), 2.29(3H,s,Me_{arom}), 2.62(1H,dd,J=7 and 12, 5a-H), 2.81(1H,septet,J=6.8, C$\underline{H}Me_2$), 7.17(1H,d,J=7, 3'-H), 7.27(1H,d,J=7, 5'-H), 7.33(1H,t,J=7, 4'-H).

Tricyclic oxazolidinone 12b: Anal. Calcd for $C_{20}H_{25}NO_4$: C,69.95; H,7.34; N,4.08%. Found: C,69.92; H,7.46; N,4.21%. MS(CI) 344(M^++1, 100%); IR(KBr) 1780cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.02(1H,m,7-H_{ax}), 1.13(3H,d,J=6.7,one of the CH$\underline{Me_2}$ remote from cyclohexane), 1.32(3H,d,J=6.7, one of the CH$\underline{Me_2}$ close to cyclohexane), 1.45(2H,m,6-H_{ax}, 8-H_{ax}), 1.70(3H,m,7-H_{eq}, 8-H_{eq}, 9-H_{ax}), 1.97(3H,s,3a-Me), 2.20(2H,m,6-H_{eq},9-H_{eq}), 2.26(3H,s,Me_{arom}), 2.71(1H,dd,J=7 and 12, 5a-H), 2.91(1H,septet,J=6.7, C$\underline{H}Me_2$), 7.18(1H,d,J=7, 3'-H), 7.27(1H,d,J=7, 5'-H), 7.33(1H,t,J=7, 4'-H).

Tricyclic oxazolidinone 13a: Anal. Calcd for $C_{21}H_{21}NO_4$: C,71.78; H,6.02; N,3.99%. Found: C,72.08; H,5.74; N,4.03%. MS(CI) 352(M^++1, 100%); IR(KBr) 1795, 1775cm^{-1}; ^{1}H-NMR($CDCl_3$) 0.82(1H,m,7-H_{ax}), 1.42(2H,m,6-H_{ax}, 8-H_{ax}), 1.73(3H,m,7-H_{eq}, 8-H_{eq}, 9-H_{ax}), 2.01(3H,s,3a-Me), 2.03(1H,m,6-H_{eq}), 2.25(1H,m,9-H_{eq}), 2.45(3H,s,Me_{arom}), 2.71(1H,dd,J=7 and 12, 5a-H), 7.42(1H,d, J=8, 3'-H), 7.49(1H,t,J=7, 6'-H), 7.53(1H,dt,J=7 and 8.4, 7'-H), 7.69(1H,d,J=8.4, 8'-H), 7.84(2H,d,J=9,4', 5'-H).

Tricyclic oxazolidinone 14: Anal. Calcd for $C_{20}H_{19}NO_4$: C,71.20; H,5.68; N,4.15%. Found: C,71.37; H,5.61; N,4.18%. MS(CI) 338(M^++1, 100%); IR(KBr) 1795, 1770cm^{-1}; ^{1}H-NMR($CDCl_3$) 0.90(1H,m), 1.35-1.85(5H,m), 2.01 and 2.03(each 1.5H,s,3a-Me), 2.05-2.30(2H,m), 2.47(0.5H,dd, J=6 and 12, 5a-H of rotamer **a**), 3.12(0.5H,dd,J=6 and 12, 5a-H of rotamer **b**), 7.29(0.5H,dd,J=1 and 8, 2'-H of rotamer **b**), 7.39(0.5H,dd,J=1 and 8, 2'-H of rotamer **a**), 7.50-7.62(3H,m), 7.72(0.5H,dd,J=1 and 8, 8'-H of rotamer **a**), 7.80(0.5H,dd,J=1 and 8, 8'-H of rotamer **b**), 7.92(1H,m), 7.97(1H,d,J=9).

Tricyclic oxazolidinone 15: Anal. Calcd for $C_{17}H_{16}F_3NO_4$: C,57.47; H,4.54; N,3.94%. Found: C,57.64; H,4.66; N,4.01%. MS(CI) 356(M^++1, 100%), 279(50), 205(74), 149(67); IR(KBr) 1770cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.00-1.50(3H,m), 1.78(1H,m), 1.90(2H,s,3a-Me of rotamer **b**), 1.97(1H,s,3a-Me of rotamer **a**), 1.95-2.30(4H,m), 2.72(0.31H,dd,J=7 and 12, 5a-H of rotamer **a**), 3.10(0.69H,t,J=7, 5a-H of rotamer **b**), 7.30(1H,m,6'-H), 7.65(1H,m), 7.70(1H,m), 7.82(1H,m).

Tricyclic oxazolidinone 16: Anal. Calcd for $C_{19}H_{23}NO_4$: C,69.28; H,7.04; N,4.25%. Found: C,69.23; H,6.94; N,4.20%. MS(CI) 330(M^++1, 100%); IR(KBr) 1780cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.03(1H,m), 1.12-1.30(6H,m,CH$\underline{Me_2}$), 1.41-1.88(5H,m), 1.96 and 1.97(total 3H,s,3a-Me), 2.04-2.22(2H,m), 2.45(0.47H,dd,J=7.6 and 12, 5a-H of rotamer **a**), 2.77(0.47H,septet,J=6.4, C$\underline{H}Me_2$ of rotamer **a**), 2.92(0.53H,septet,J=7.6, C$\underline{H}Me_2$ of rotamer **b**), 3.02(0.53H,dd,J=7 and 11, 5a-H of rotamer **b**), 7.00(0.53H, d,J=7, 6'-H of rotamer **b**), 7.12(0.47H,d,J=7, 6'-H of rotamer **a**), 7.26(1H,m), 7.46(2H,m).

Tricyclic oxazolidinone 17: Anal. Calcd for $C_{22}H_{21}NO_4$: C,72.71; H,5.82; N,3.85%. Found: C,72.88; H,5.72; N,3.91%. MS(CI) 364(M^++1, 100%); IR(KBr) 1795, 1770cm^{-1}; ^{1}H-NMR($CDCl_3$) 0.80-1.00(2H,m), 1.05-1.45(3H,m), 1.47(1.65H,s,3a-Me of rotamer **b**), 1.55-2.10(3H,m), 1.83(1.35H,s,3a-Me of rotamer **a**), 2.15(0.45H,dd,J=6 and 12, 5a-H of rotamer **a**), 2.93(0.55H,t,J=6, 5a-H of rotamer **b**), 7.24(1H,m, 6'-H), 7.45(8H,m).

Tricyclic oxazolidinone 18: Anal. Calcd for $C_{17}H_{19}NO_4$: C,67.76; H,6.36; N,4.65%. Found: C,67.56; H,6.23; N,4.60%. MS(CI) 302(M^++1, 100%); IR(KBr) 1800, 1760cm^{-1}; ^{1}H-NMR($CDCl_3$)

Table 2 ^{13}C-NMR Data of Tricyclic Oxazolidinones **12-20**. Chemical shifts in ppm, *J* value in Hz, solvent $CDCl_3$.[a)]

Compound	3a-Me	C-6,7,8 and 9				C-5a	C-9a	C-3a	C-2	C-5	Substituents
12a	21.32	21.71 (C-7)	22.26 (C-8)	26.94 (C-6)	27.10 (C-9)	43.78	71.65	110.44	153.25	173.83	20.12(2'-Me), 22.37(one of the CH<u>Me2</u> close to 5a-H), 26.70(one of the CH<u>Me2</u> remote from 5a-H), 29.22(CH), 125.16(C-5'), 128.42(C-1'), 129.52(C-3'), 129.79(C-4'), 139.04(C-2'), 150.00(C-6').
12b	21.18	21.65 (C-7)	22.24 (C-8)	26.65 (C-6)	27.24 (C-9)	44.26	71.16	110.33	153.25	174.10	19.51(2'-Me), 22.84(one of the CH<u>Me2</u> close to cyclohexane), 26.06(one of the CH<u>Me2</u> remote from cyclohexane), 29.46(CH), 125.16(C-5'), 128.69(C-1'), 129.53(C-3'), 129.77(C-4'), 138.50(C-2'), 150.22(C-6').
13a	21.26	21.57 (C-7)	22.14 (C-8)	26.53 (C-6)	26.98 (C-9)	44.91	72.21	110.45	153.19	174.04	20.12(2'-Me), 122.34(C-8'), 126.01(C-6'), 126.54, 127.55(C-7'), 128.23(C-4' or 5'), 129.10(C-3'), 129.80(C-4' or 5'), 132.52, 133.25, 137.77(C-2').
14	21.01	21.85	22.02	26.13	27.49	44.15	70.45	110.53	153.29	173.59	121.96, 122.99, 125.18, 125.51, 126.77, 127.05, 127.47, 128.13, 128.69, 128.82,
	21.32	21.93	22.18	26.57	27.76	44.99	70.57	110.64	153.64	173.99	129.07, 129.13, 129.30, 129.79, 130.60, 130.65, 131.89, 131.97, 134.78, 134.91.
15	18.92	19.65	21.55	26.16		43.06	68.62	109.59	152.31	173.09	123.12(CF_3, q, J_{CF}=272), 123.34(CF_3, q, J_{CF}=272), 128.37(CH), 128.66(C-2'),
	20.89	21.40	25.30	27.01		43.82	70.68	110.37	153.12	173.94	130.56(CH), 130.63(CH), 130.66(CH), 131.92(CH), 132.03(CH), 133.80(CH), 134.28(CH), 134.95(CH).
16	20.83	21.54	22.06	25.72	27.74	43.57	69.63	110.09	153.12	173.50	23.21(Me), 23.47(Me), 24.70(Me), 25.23(Me), 28.18(CH), 28.52(CH), 126.60(CH),
	21.30	21.66	22.14	26.68		44.99	69.84	110.37	153.44	173.61	126.93(CH), 127.79(CH), 127.89(CH), 129.67(C-1'), 129.74(C-1'), 130.16(CH), 130.21(CH), 130.33(CH), 131.36(CH), 149.44(C-2'), 149.79(C-2').
17	19.38	20.09	21.19	23.12	26.21	42.75	68.97	109.55	154.51	171.49	128.01(CH), 128.32(CH), 128.41(CH), 128.54(CH), 128.66(CH), 128.87(CH),
	21.19	20.91	21.81	26.13	26.89	44.76	70.38	109.64	155.04	173.38	129.03(CH), 129.07(CH), 129.21(CH), 130.07(CH), 130.20(CH), 130.86(CH), 131.48, 131.83(CH), 132.43(CH), 133.20(CH), 138.16, 139.14, 143.39, 143.55.
18	20.02	20.54	21.30	24.39	25.69	43.34	69.71	110.02	151.90	173.50	17.30(2'-Me), 17.99(2'-Me), 126.86, 127.06, 129.33, 129.39, 129.95, 131.53,
	20.43	20.87	21.67	25.62	26.97	44.29	69.84	110.40	152.30	173.86	131.58, 131.67, 131.80, 138.04, 138.33.
19	20.98	21.95 (C-8)	22.11 (C-7)	26.39 (C-6)	27.83 (C-9)	43.69	69.51	110.31	153.38	173.86	55.41(OMe), 112.40(C-3'), 121.05(C-5'), 121.40(C-1'), 131.40(C-4'), 132.17(C-6'), 156.95(C-2').
20	20.85	21.69 (C-7)	21.82 (C-8)	25.99 (C-6)	26.54 (C-9)	44.35	69.75	110.30	152.87	173.06	117.24(C-3',d, J_{CF}=20.1), 120.58(C-1', d, J_{CF}=12.8), 125.36(C-6', d, J_{CF}=3.7), 131.98(C-4', d, J_{CF}=7.3), 132.41(C-5'), 159.61(C-2', d, J_{CF}=250.5).

a) For compounds **12a**,**12b**,**13a**,**19**, and **20**, assignments were carried out by CH-COSY, HH-COSY, and NOE experiments. Complete assignments for compounds **14-18** were difficult due to very close signals of rotamers.

1.06(1H,m), 1.52(3H,m), 1.76(2H,m), 1.96(3H,s,3a-Me), 2.10(2H,m), 2.23 and 2.30(each 1.5H, s,Me_{arom}), 2.50(0.48H,dd,J=7 and 12, 5a-H of rotamer **a**), 3.05(0.52H,dd,J=7 and 12, 5a-H of rotamer **b**), 7.04(0.52H,d,J=7, 6'-H of rotamer **b**), 7.15(0.48H,d,J=7, 6'-H of rotamer **a**), 7.26(1H,m), 7.35(2H,m).

Tricyclic oxazolidinone 19: Anal. Calcd for $C_{17}H_{19}NO_5$: C,64.34; H,6.03; N,4.41%. Found: C,64.23; H,5.84; N,4.36%. MS(CI) 318(M^++1, 100%); IR(KBr) 1800-1750 br cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.02(1H,m,7-H_{ax}), 1.45(2H,m,6-H_{ax} and 8-H_{ax}), 1.75(3H,m,7-H_{eq}, 8-H_{eq}, 9-H_{ax}), 1.95(3H,s,3a-Me), 2.16(2H,m,6-H_{eq},9-H_{eq}), 2.48(1H,br s,5a-H), 3.78(3H,s,OMe), 7.02(2H,m,3',5'-H), 7.15(1H,d,J=7, 6'-H), 7.43(1H,t,J=7, 4'-H).

Tricyclic oxazolidinone 20: Anal. Calcd for $C_{16}H_{16}FNO_4$: C,62.95; H,5.28; N,4.59%. Found: C,63.10; H,5.13; N,4.62%. MS(CI) 306(M^++1, 100%); IR(KBr) 1800-1760 br cm^{-1}; ^{1}H-NMR($CDCl_3$) 1.05(1H,m), 1.50(2H,m), 1.73(3H,m), 1.96(3H,s,3a-Me), 2.18(2H,m), 2.78(1H,dd,J=7 and 12, 5a-H), 7.21(1H,t,J=7), 7.25(2H,m), 7.48(1H,m).

Lineshape Analysis of the Dynamic NMR Spectra for Compound 19: Lineshapes of the exchange-broadened spectra of the OMe signals in the temperature range from -50°C to 20°C (in steps 10 degree) were simulated by using the SITE2V program[14] to obtain the rate constants for the internal rotation about the N-C bond. Least-squares analyses of Arrhenius plots of the rate constants afforded the E_A value to be 14.4 ± 0.7 kcal/mol (r>0.999). Table 3 shows the kinetic parameters of this compound.

Table 3. Rate Constants for the Rotation of Compound **19**.

T (°C)	k (s^{-1})	$\Delta G^{\ddagger}$ (kcal/mol)
-50	0.67	13.1
-40	2.5	13.1
-30	10.5	13.0
-20	25	13.1
-10	83	13.0
0	200	13.0
10	670	12.9
20	1670	12.8

At 0°C, following data were calculated.
$\Delta G^{\ddagger}$ = 13.0 kcal/mol.
$\Delta H^{\ddagger}$ = 13.9 ± 0.7 kcal/mol.
$\Delta S^{\ddagger}$ = 3.3 ± 2.6 eu.
log$A$ = 13.9 ± 0.6.

Determination of the Rate Constants k for Compound 18 by the Saturation Transfer Method: When two rotamers A and B are present in solution, the rate constants k_A and T_{1A} can be obtained from the simultaneous equation (2).

$$[A] \underset{k_B}{\overset{k_A}{\rightleftharpoons}} [B] \qquad k_A[A] = k_B[B] \qquad (1)$$

$$M_A / M_{0A} = 1 / (1+k_A T_{1A}) \qquad 1 / T_{1Aeff} = 1 / T_{1A} + k_A \qquad (2)$$

[A], Concentration of rotamer A; [B], Concentration of rotamer B; M_A / M_{0A}, ratio of remaining magnetization under saturation transfer conditions; T_{1Aeff}, observable longitudinal relaxation time; T_{1A}, theoretical longitudinal relaxation time.

The method involves selectively perturbing the magnetization of one site with a weak saturating field and then measuring the T_{1Aeff} value of the other site by the inversion recovery method. The value of M_A / M_{0A} can be obtained by comparison of the steady-state intensity with a saturated field and a nonsaturated field. From these values, the rate constants k_A and k_B were calculated.

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8. The tricyclic compounds **12-20** possess both chiral centers and chiral axis. Since our starting material **2** is racemic, the nomenclature of these compounds should be (3a*RS*,5a*RS*,9a*RS*)-1-aryl-3a-methyl-1,2,5,5a,6,7,8,9-octahydro-3a*H*-isobenzofuro[7a,1-*d*]oxazol-2,5-dione, and only 3a*S*-form is shown in Scheme 2. As for the chiral axis of the benzene ring, it should be (*RS*) if R^1precedes R^3. For the expediency of discussion, the rotamers are indicated by adding subscripts **a** and **b** to their compound number. Thus **12** indicates a mixture of rotamers and **12a** indicates one of the rotamers whose preceding substituent (*i*-Pr) is oriented to site A as shown in Scheme 1.
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14. The PC version of two site exchange simulation program was kindly provided from Prof. J. T. Gerig in University of California, Santa Barbara.