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A Highly Diastereoselective Tandem Michael-Michael Addition Reaction in a Rotameric Ring System: Steric Acceleration due to Conformation Locking

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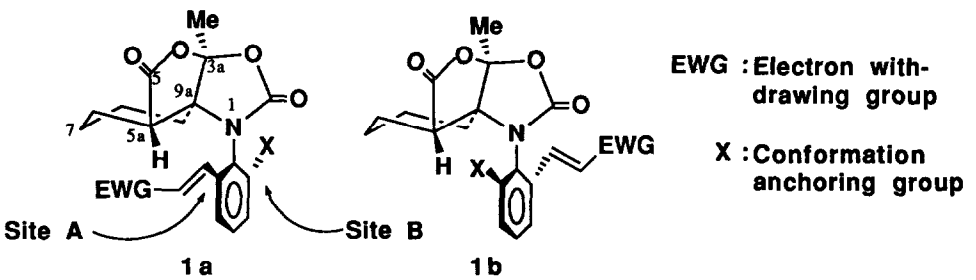
Abstract A highly diastereoselective one-pot tandem Michael-Michael addition reaction developed in a rotamerically locked conformation is described Reaction of isocyanates **8** - **13** with hydroxylactone **14** gave tandem Michael-Michael adducts **22** - **26** in good to excellent yields The intermediate tricyclic oxazolidinones consisted of rotamer pairs **16** - **19**, and the rotation barriers of some of these compounds were determined The tandem addition reaction was highly accelerated by introducing conformation anchoring group X A new versatile synthesis of octahydroacridines **27** - **29** using the tandem adducts is also described

Locking of the conformation of the reaction center to a desired form is a pivotal subject for building up a molecule stereoselectively Synthetically, such a conformation locking has often been accomplished by using a low reaction temperature and/or complexation with metals to restrict the bond rotation In view of conformation locking, studies on the reactivity of stable rotamers would provide a model for understanding the relation between the reactivity and the conformational flexibility of the functional groups [2] In rotameric systems, several groups have reported that remarkable differences in reactivity exist between the rotamers in haloacetamides,[3] fluorenes,[4] triptycenes,[5] and aryldi-*t*-butylcarbinols [6] Since the successful preparation[7] and isolation of stable rotamer pairs at room temperature[8] in the isobenzofuro[7a,1-*d*]oxazole ring system, we naturally became interested in the reactivity of this skeleton As shown in Scheme 1, this skeleton involves a nucleophilic center



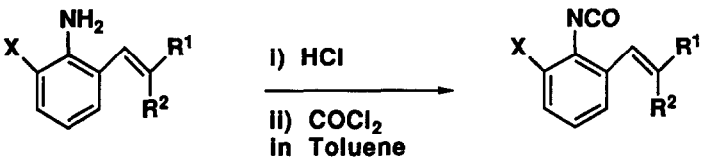
Scheme 1

at C - 5a of the cyclohexane ring [9] If an electrophilic center is present in one of the *ortho* di-substituents on the benzene ring, it is hoped that the bulkiness of the conformation anchoring group X would govern the reactivity of the subsequent Michael addition Based on this viewpoint, we investigated the intramolecular Michael addition between the electrophilic center on the *ortho* substituent of the benzene ring and the nucleophilic center (C - 5a) of the cyclohexane ring

In this report, we describe mainly three aspects The first topic is a one-pot, diastereoselective tandem Michael-Michael reaction which controls the relative configuration of four contiguous asymmetric centers, three of which are quaternary The second is a steric acceleration due to the rotameric conformation locking in the Michael reaction The third is a synthetic application of the tandem adduct to the preparation of the octahydroacridine skeleton

RESULTS AND DISCUSSION

At first, we prepared 2'-aminocinnamates having *E* configuration Because the corresponding *Z* isomers are often difficult to obtain in pure form due to their energetically unfavorable configuration and have been reported to cyclize easily to the carbostyril derivatives under acidic conditions [10] The requisite (*E*)-2'-isocyanatocinnamates **8** - **13** were easily prepared by reacting the corresponding (*E*)-2'-aminocinnamates **2** - **7** [10b, 11] with phosgene [12] The stereochemical configuration of all of the olefinic moiety in compounds **8** - **13** was determined to be *E* by the coupling constants of the olefinic protons in the ^{1}H NMR spectra



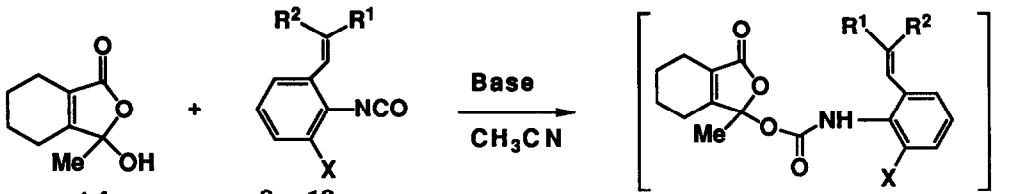
Scheme 2 **2 - 7** **8 - 13**

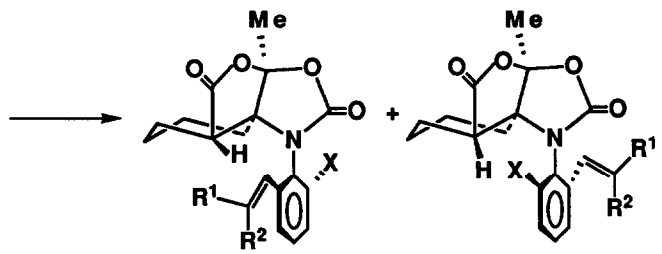
Table 1 Preparation of (*E*)-2'-isocyanatocinnamates or corresponding nitrile **8** - **13**

Starting material	Product	R^1	R^2	X	Yield (%)	mp °C bp (°C/mmHg)
2	**8**	COOMe	H	H	68	55-6 (128-9/2)
3	**9**	CN	H	H	49	49-51 (133-5/2)
4	**10**	COOMe	Me	H	59	(131-2/2)
5	**11**	COOMe	H	OMe	84	116-7[a)]
6	**12**	COOMe	H	Cl	52	115-7[a)]
7	**13**	COOMe	H	Me	70	48-9[a)]

[a)] Recrystallized from Et_2O - *n*-hexane

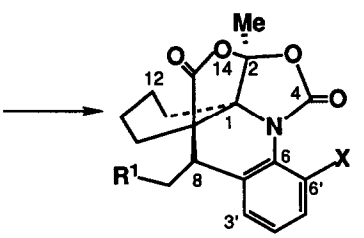
The transformations outlined in Scheme 3 demonstrate our sequential Michael addition reaction Initial feasibility studies were conducted with the reaction of hydroxylactone **14** and isocyanate **8** in acetonitrile at room temperature. As expected, the tricyclic oxazolidinone **16** was obtained in 83% yield in the presence of 5 mol% of triethylamine (TEA). None of the tandem adduct **22** was found in the crude reaction mixture The ^{1}H NMR spectrum of compound **16** in $CDCl_3$ showed the presence of a rotamer pair **16a** and **16b** in the ratio of approximately 1 2 The stereochemical relation was elucidated by NOE study, in which we detected clear saturation transfer from the irradiated signal of one rotamer to the other rotamer signal Thus these rotamers are inseparable at room temperature. The rate constants of interconversion (k_A, k_B) between **16a** and **16b** were



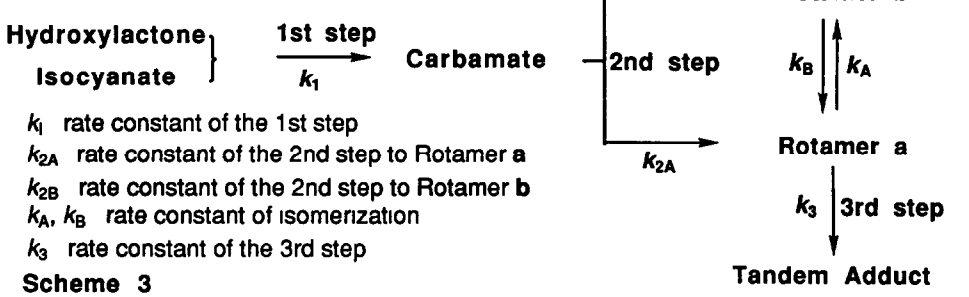


	R^1	R^2	X
16	CO_2Me	H	H
17	CN	H	H
18	CO_2Me	Me	H
19	CO_2Me	H	OMe
20	CO_2Me	H	Cl
21	CO_2Me	H	Me

Compounds **20** and **21** were not isolated



	R^1	X
22	CO_2Me	H
23	CN	H
24	CO_2Me	OMe
25	CO_2Me	Cl
26	CO_2Me	Me



k_1 rate constant of the 1st step
k_{2A} rate constant of the 2nd step to Rotamer **a**
k_{2B} rate constant of the 2nd step to Rotamer **b**
k_A, k_B rate constant of isomerization
k_3 rate constant of the 3rd step

Scheme 3

determined by the saturation transfer method.[13] From these data, we estimated the barrier to conversion of **16a** to **16b** to be $\Delta G^{\ddagger}$ = 17 6 kcal/mol and that to the reverse process to be $\Delta G^{\ddagger}$ = 17 9 kcal/mol at 25 °C As we have already reported,[8] the barrier to rotation about the N - C bond for the *ortho*-OMe derivative of this skeleton is $\Delta G^{\ddagger} \approx$ 13 kcal/mol and that of the *ortho*-Me derivative is $\Delta G^{\ddagger} \approx$ 19 kcal/mol Therefore, the bulkiness of the acrylic moiety in compound **16** is considered to be larger than that of the OMe group to some extent and slightly smaller than that of the Me group with respect to the rotational behavior

On the contrary, when this reaction was conducted in the presence of a stronger base catalyst such as 5 mol% of 1,8-diazabicyclo[5 4 0]undec-7-ene (DBU) or 5 mol% of K_2CO_3 with 1 mol% of 18-Crown-6, the intermediate **16** was completely consumed and the tandem Michael-Michael adduct **22** was obtained in 60% and 68% yield, respectively The reaction proceeded quite diastereoselectively, because we could not detect the formation of other stereoisomers It is obvious that the tandem adduct **22** is formed only from the rotamer **16a** and not from **16b** Since the rotational barrier of compound **16** is not high enough to prevent the interconversion between the rotamers under the reaction conditions,[14] the formation of the tandem adduct **22** is considered to be the result of equilibrium control This successful result of the tandem addition prompted us to investigate the general applicability of this reaction Table 2 shows the summary of the results

Table 2 Reaction of hydroxylactone **14** with isocyanates **8** - **13** in acetonitrile at room temperature

Starting material	Reaction time (h)	Base[a]	Products: Tricyclic adduct	Products: Tandem adduct	Yield (%)	mp[d] (°C)
8	16	TEA	**16**	-	83	207-8
	24	DBU	-	**22**	60	204-5
	16	K_2CO_3[b]	-	**22**	68	
9	48	TEA	**17**	-	51	232-3
	24	DMAP	**17**	-	43	
	48	DBU	-	**23**	38	285-7
	5	K_2CO_3[b]	-	**23**	43	
10	24	DBU	**18**	-	57	162-3
11	48	TEA	**19a, 19b**	**24**	46[c]	231-2[e]
	16	DBU	**19b**	**24**	83[c]	
12	16	TEA	-	**25**	86	228-9
	3	DBU	-	**25**	86	
13	16	TEA	-	**26**	80	221-2
	3	DBU	-	**26**	77	

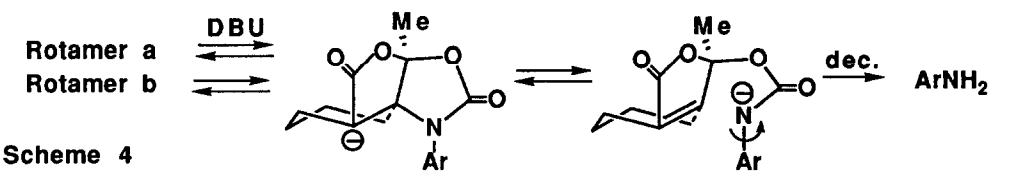
a) The amount of TEA, DBU, or DMAP (4-*N*,*N*-dimethylaminopyridine) used was 5 mol% b) The amount of K_2CO_3 used was 5 mol% with 1 mol% of 18-Crown-6 In the absence of 18-Crown-6, the reaction was very slow c) Yield of tandem adduct **24** Compounds **19a** (32%) and **19b** (8%) were isolated using TEA as a catalyst, and the rotamer **19a** remained (20%) even stirred for one week at room temperature Compound **19b** (8%) was isolated using DBU as a catalyst and **19a** was completely converted to **24** d) Recrystallized from Et_2O-$CHCl_3$ except for compound **23** Compound **23** was recrystallized from $CHCl_3$ e) Mp of compound **24**

Reaction of isocyanate **9** and **14** gave the tricyclic oxazolidinone **17** (TEA or DMAP as a catalyst) and the tandem adduct **23** (DBU or K_2CO_3 as a catalyst), although the yields were somewhat lower than those of **8** and **14** In case of isocyanate **10**, we could easily obtain the tricyclic compound **18** However, compound **18** did not give the tandem adduct even under a severe reaction condition (at 60 °C for 6 h using DBU as a catalyst) and gradually decomposed to give aniline **4** and some unidentifiable materials The rotational barriers for compounds **17** and **18** were considered nearly equal to that of compound **16**, because we did observe saturation transfer in the NOE experiments of these compounds at 25 °C

We next intended to restrict the rotation about the N-C bond more rigidly to lock the conformation of the reaction center of the tandem Michael addition by introducing another *ortho*-substituent X To our surprise, the introduction of the substituent X significantly changed the reactivity of the subsequent Michael addition

Treatment of **11** and **14** with TEA catalyst in acetonitrile gave three products which were easily separated by column chromatography Two of them were identified to be the tricyclic oxazolidinone **19a** (32%) and **19b** (8%) and the third component was the tandem adduct **24** (46%) The stereochemical structures of these compounds were elucidated by NOE experiments When each of the pure compounds **19a** or **19b** was heated above its melting point for 1 min , we obtained the rotamer mixture in a ratio of approximately **19a** **19b** = 3 7 in both cases. Therefore, compounds **19a** and **19b** are a rotamer pair due to the restricted rotation about the N - C bond The barriers to rotation were determined by measuring the rate constants of thermal isomerization of each rotamer From the data, the barrier to rotation of the **19a** to **19b** process was estimated to be $\Delta G^{\ddagger}$ = 29 4 kcal/mol, that to the reverse process to be $\Delta G^{\ddagger}$ = 30 5 kcal/mol at 111 °C and the equilibrium constant K = **a/b** = 0 25 in favor of rotamer **19b** In the case of DBU catalyst, the reaction of **11** and **14** gave the tandem adduct **24** in 83% yield, together with rotamer **19b** in 8% yield

Although the barriers to rotation of rotamers **19a** and **19b** are high enough to prevent the isomerization at room temperature, we examined the possibility of DBU-catalyzed isomerization of these compounds by using NMR Treatment of pure **19a** with 5 mol% of DBU in CD_3CN at room temperature for 20h gave a mixture of **24** **19b** aniline **5**=85 4 11 After 90h, the reaction slowly proceeded and the ratio was **24** **19b** **5**=86 2 12 Similarly, treatment of pure **19b** gave a mixture of **24** **19b** **5**=20 70 10 (after 20h) and **24** **19b** **5**=60 20 20 (after 90h) In both cases, rotamer **19a** was completely converted to **24** Therefore, DBU-catalyzed slow isomerization really exist in these reactions This isomerization and aniline formation should be attributable to the *retro*-Michael addition of rotamers as shown below As the rate of isomerization is slow, we believe that the tandem reaction proceeds mainly under the kinetically controlled condition [15]



Scheme 4

Experimental results of the reactions of isocyanates **12** or **13** with hydroxylactone **14** were very simple We obtained the tandem adducts **25** or **26** in high yields not only using DBU as a catalyst but also even using TEA as a catalyst We checked the by-product distribution in these reactions However, we could detect only the formation of small amounts of anilines **6** or **7**, but none of the rotamers **20** or **21** were found in the reaction mixture Although the reason for the site selectivity in this reaction is not clear at present, these results suggest

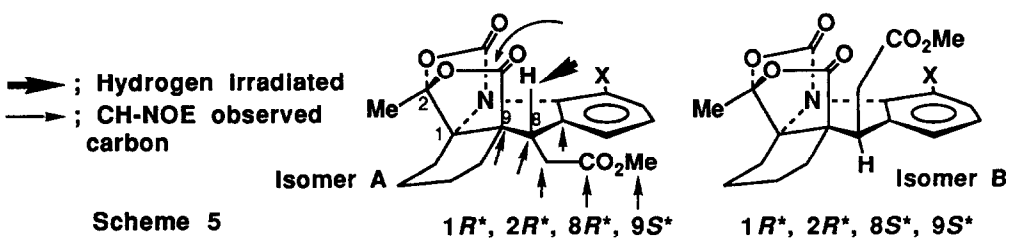
that the site selectivity of the initial Michael addition is highly biased toward the rotamers **20a** or **21a** Because, as in the case of compound **19**, the rotation barriers of compounds **20** or **21** are considered to be very high, one of the rotamers **20b** or **21b** should be obtained if the site selectivity is not so highly biased

Therefore, we next tried to isolate the rotamers **20a** or **21a** by quenching the reaction before the completion of the tandem reaction We carried out the reaction of **13** and **14** with TEA catalyst and quenched the reaction after 2 h by adding acetic acid The ^{1}H NMR analysis of the crude reaction mixture followed by column chromatography revealed the formation of carbamate **15** (50%) and the tandem adduct **26** (25%) Although the starting materials, **13, 14**, and the formation of small amounts of unidentifiable materials were detected, *none of the intermediate tricyclic compound 21 was found!*

These observations can be rationalized as follows Our sequential reactions consist of three bond-forming steps The first step is the carbamate formation, the second step is the tricyclic oxazolidinone formation and the third step is the C-C bond formation giving the final adduct as shown in Scheme 3

In the case where the conformation anchoring group was very small (X = H), we could not obtain the tandem adducts **22** or **23** in the TEA-catalyzed reaction Therefore, k_3 should be zero and if we wish to prepare **22** under TEA-catalyzed conditions, the rate determing step is the third step In the case of a larger anchoring group (X = OMe), k_3 became large because we could obtain the tandem adduct **24** in moderate yield even using TEA as a catalyst. When the conformation anchoring group is large enough (X = Me or Cl), the reaction rate of the third step becomes much larger Once tricyclic adducts **20** or **21** are formed, their barriers to rotation about the N - C bonds are considered to be higher than that of compound **19** because the Me or Cl group is bulkier than the OMe group [16] Their nucleophilic and electrophilic reaction centers are then spatially very close, and their conformational movements are much more restricted than that of compound **19** by the conformation anchoring group X Thus the subsequent Michael addition is highly accelerated (k_3 becomes very large), and the reaction can proceed even using a weak base catalyst such as TEA, resulting in high yields Consequently, the lifetime of the intermediate rotamers **20** or **21** becomes too short to isolate them These results are new examples of steric acceleration due to the conformation locking

The stereochemical configuration of C-8 of the tandem adducts **22** - **26** was determined by the CH-NOE study Irradiation of 8-H enhanced the signals of C-7, C-8, C-9, 8-CH_2, C-15, and CO_2Me If the location of 8-H is on the opposite side of the lactone ring like isomer B, the NOE would never be observed between 8-H and C-15 Therefore, the stereochemical structure was determined to be isomer A as shown in Scheme 5 We reconfirmed the stereochemistry of the tandem adduct by X-ray crystallographic analysis of compound **24** as shown in Figure 1 The asymmetric unit of this crystal consisted of a pair of 1*R* and 1*S* isomers Thus, we determined the relative configuration of the asymmetric centers of the tandem adducts **22** - **26** to be 1*R**, 2*R**, 8*R** and 9*S**, and only the 1*S* form is shown in this paper These results suggest that the tandem addition proceeds *via* energetically favorable *s* - trans conformation in the C_{arom}-CH= bond of the olefinic moiety



Scheme 5

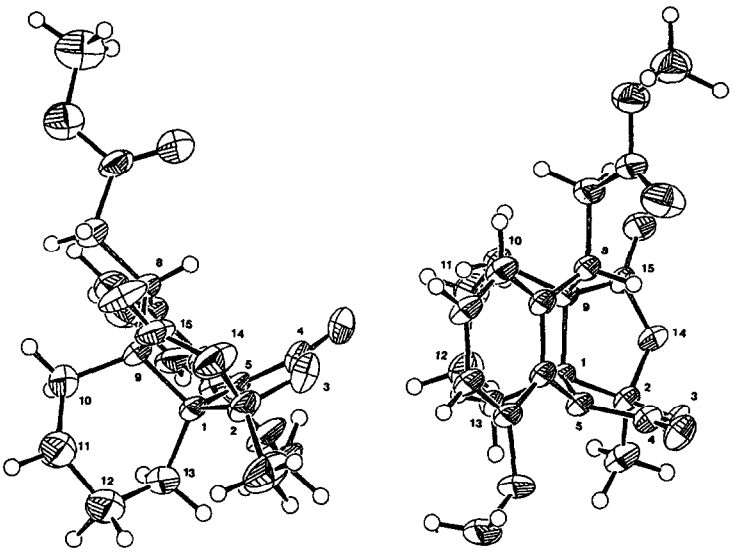
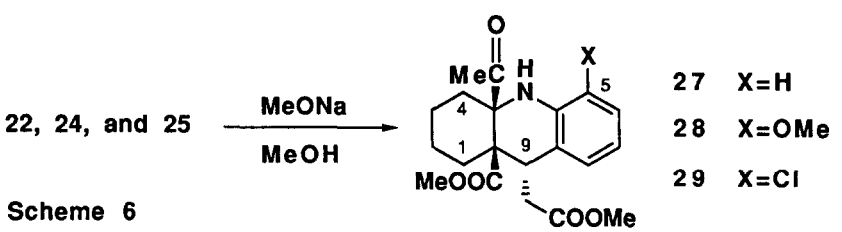


Figure 1 Computer generated crystal structure for compound **24.**

Since the tandem Michael-Michael adducts have many functional groups of their own, we sought the synthetic utility of these compounds We studied the base-promoted cleavage of the oxazolidinone ring of the tandem adduct [17] After several trials, we found that cleavage of the oxazolidinone ring proceeded cleanly by merely heating the tandem adduct in the presence of an equimolar amount of NaOMe in MeOH to afford the octahydroacridine in high yield The stereochemistry of the octahydroacridines **27** - **29** were also determined by CH-NOE and NOESY measurements By the irradiation of 9-H, we observed enhancements at C-4a, C-8a, C-9, C-9a, C-10a, and both ester OMe groups In NOESY measurement, 4a-acetyl Me group showed cross peaks between 9-H and 9a-CO_2Me Therefore, the location of 9-H is on the same side of the 4a-acetyl and 9a-CO_2Me groups



Scheme 6

Conceptually, the chemistry described here provides a new model for the conformation locking of the reaction center For synthetic purposes, sequential C - N followed by a C - C bond-forming process would provide a useful methodology for building up a new nitrogen-containing heterocyclic ring system Moreover, it should be noted that quaternary centers are also easily formed by this methodology We are currently investigating extension of the reactions in this rotameric system

EXPERIMENTAL SECTION

Commercially available chemicals were of reagent grade, and used without further purification unless otherwise stated Acetonitrile was dried over molecular sieves 3A Melting points were determined on a hot stage apparatus, and were uncorrected IR spectra were recorded on a SHIMADZU IR-440 spectrophotometer NMR spectra were recorded on a Varian Gemini200 (200MHz), or a JEOL JNM-GSX400 (400MHz) 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

General Procedure for the preparation of (*E*)-2'-isocyanatocinnamates or cinnamonitrile (8 - 13): *Caution, Phosgene is highly toxic The reaction should be carried out in a well-ventilated hood* To a stirred solution of aniline (2 - 7) (50 mmol) in toluene (100 mL) was introduced hydrogen chloride for 20 min under ice-cooling. The resulted suspension of the aniline hydrochloride was heated to 90°C and phosgene (generated by the dropwise addition of trichloromethyl chloroformate (15 mL) to active charcoal (1 g)) was introduced during 2 - 4 h to this suspension After cooling, toluene was removed under reduced pressure Et_2O was added to the residue and insoluble materials were filtered off The Et_2O soluble portion was concentrated and purified by distillation or recrystallization

Methyl (*E*)-2'-isocyanatocinnamate (8): IR(KBr) ν 2280(NCO), 1720(C=O)cm^{-1}, ^1H NMR($CDCl_3$) δ 3 82(s, 3H, OMe), 6 46(d, J=16, 1H, =CHCO), 7 18(m, 2H, 3'-H, 4'-H), 7 33(dt, J=1 5 and 8, 1H, 5'-H), 7 57(dd, J=1 5 and 8, 6'-H), 7 94(d, J=16, 1H, C_{arom}-CH=), ^{13}C NMR($CDCl_3$) δ 51 78(OMe), 119 96(CH), 126 04(CH), 126 88(CH), 127 35(CH), 128 77, 131 08(CH), 132 76, 139 38(CH), 166 95(C=O), MS(CI) m/z 204(M^++1, 100%), 146(24), Anal Calcd for $C_{11}H_9NO_3$ C, 65 02, H, 4 46, N, 6.89% Found C, 65 15, H, 4 50, N, 7 13%

(*E*)-2'-Isocyanatocinnamonitrile (9): IR(KBr) ν 2250(NCO), 2210(CN)cm^{-1}, 1H NMR($CDCl_3$) δ 5 95(d, J=16, 1H, =CHCN), 7 20(m, 2H), 7 40(dt, J=1 7 and 7 7, 1H, 5'-H), 7 50(dd, J=1 7 and 7 7, 1H, 6'-H), 7 66(d, J=16, 1H, C_{arom}-CH=), ^{13}C NMR($CDCl_3$) δ 98 47(CH), 117 86(CN), 126 29(CH), 126 75(CH), 127 24(CH), 127 75, 132 12(CH), 132 80, 145 44(CH), MS(CI) m/z 171(M^++1, 80%), 145(56), Anal Calcd for $C_{10}H_6N_2O$ C, 70 58, H, 3 55, N, 16 46% Found C, 70 98, H, 3 79, N, 16 86%

Methyl (*E*)-2'-isocyanato-2-methylcinnamate (10): IR(Neat) ν 2280(NCO), 1720(C=O)cm^{-1}, ^1H NMR($CDCl_3$) δ 2 01(d, J=1 5, 3H, Me), 3 83(s, 3H, OMe), 7 12-7 35(m, 4H), 7 71(q, J=1 5, 1H, -CH=), ^{13}C NMR($CDCl_3$) δ 14 09(Me), 52 13(OMe), 125 48(CH), 125 57(CH), 129 31(CH), 129 83(CH), 131 10, 131 26, 132 37, 134 38(CH), 168 24(C=O), MS(CI) m/z 218(M^++1, 42%), 192(45), 160(100), Anal Calcd for $C_{12}H_{11}NO_3$ C, 66 35, H, 5 10, N, 6 45% Found C, 66 74, H, 4 90, N, 6 47%

Methyl (*E*)-2'-isocyanato-3'-methoxycinnamate (11): IR(KBr) ν 2260(NCO), 1715(C=O), 1640cm^{-1}, ^1H NMR($CDCl_3$) δ 3 81(s, 3H, CO_2Me), 3 96(s, 3H, OMe), 6 48(d, J=16, 1H, =CHCO), 6 89(dd, J=7 and 2 6, 1H, 4'-H), 7 15(m, 2H, 5' and 6'-H), 7 98(d, J=16, 1H, C_{arom}-CH=), ^{13}C NMR($CDCl_3$) δ 51 58(ester OMe), 56 04(OMe), 111 79(C-4'), 112 60(C-2'), 119 14(CH), 119 95(CH), 124 03(NCO), 125 76(C-5'), 128 95(C-1'), 140 18(C_{arom}-CH=), 154 31(C-3'), 167 69(C=O), MS(CI) m/z 234(M^++1, 100%), 190(14), Anal Calcd for $C_{12}H_{11}NO_4$ C, 61 79, H, 4 75, N, 6 01% Found C, 61 64, H, 4 70, N, 6 00%

Methyl (*E*)-3'-chloro-2'-isocyanatocinnamate (12): IR(KBr) ν 2260(NCO), 1715(C=O)cm^{-1}, ^{1}H NMR($CDCl_3$) δ 3 83(s, 3H, CO_2Me), 6.47(d, *J*=16, 1H, =CHCO), 7 15(t, *J*=7 7, 1H, 5'-H), 7 46(m, 2H, 4' and 6'-H), 7.96(d, *J*=16, 1H, C_{arom}-CH=), ^{13}C NMR($CDCl_3$) δ 51.75(OMe), 121 16(CH), 125 91(CH), 126 42(CH), 130 81, 131 07(CH), 131 48(CH), 132.67(CH), 139 74(CH), 167 28(C=O), MS(CI) m/z 238(M^++1, 100%), 240(M^++3, 35%), 180(53), Anal Calcd for $C_{11}H_8ClNO_3$· C, 55 60, H, 3 39, N, 5.89%. Found: C, 55 41, H, 3 47, N, 6 14%

Methyl (*E*)-2'-isocyanato-3'-methylcinnamate (13): IR(KBr) ν 2280(NCO), 1710(C=O)cm^{-1}, ^{1}H NMR($CDCl_3$) δ 2.38(s, 3H, Me), 3 83(s, 3H, CO_2Me), 6 44(d, *J*=16, 1H, =CHCO), 7 12(t, *J*=8, 1H, 5'-H), 7 24(d, *J*=8, 1H, 6'-H), 7 43(d, *J*=8, 1H, 4'-H), 7 99(d, *J*=16, 1H, C_{arom}-CH=), ^{13}C NMR($CDCl_3$) δ 18 37(Me), 51 60(OMe), 120 13(CH), 125 08(CH), 126 00(CH), 129 34, 132 04, 132 45(CH), 134 82, 140 33(CH), 167 52(C=O), MS(CI) m/z 218(M^++1, 100%), 160(40), Anal Calcd for $C_{12}H_{11}NO_3$ C, 66 35, H, 5 10, N, 6 45% Found C, 66 21; H, 5 16, N, 6 75%

General Procedure for the preparation of Compounds 16 - 26 To a stirred solution of hydroxylactone[7] **14** (5 mmol) and isocyanate **8 - 13** (5 mmol) in anhydrous acetonitrile (10 mL) was added an appropriate catalyst (0 25 mmol) at room temperature The reaction was monitored by *TLC* or ^{1}H NMR spectroscopy After the reaction had finished, several drops of acetic acid was added and acetonitrile was removed under reduced pressure The residue was dissolved in small quantity of $CHCl_3$ followed by gradual addition of Et_2O to give compounds **16 - 26** For the separation of rotamers **19a, 19b**, and tandem adduct **24**, the residue was chromatographed on silica-gel (eluent $CHCl_3$ AcOEt = 20 1)

Methyl (*E*)-(3a*R,5a*R**,9a*R**)-2'-(2,5-dioxo-3a-methyl-1,2,5,5a,6,7,8,9-octahydro-3a*H*-isobenzofuro[7a,1-*d*]oxazol-1-yl)cinnamate (16):**

inseparable rotamer mixture a b=1 2, IR(KBr) ν 1770(C=O), 1720(C=O)cm^{-1}, ^{1}H NMR($CDCl_3$) δ 1 03(m, 1H, 7-H_{ax}), 1 40-1 80(m, 5H, 7-H_{eq}, 8-H_2, 6-H_{ax}, 9-H_{ax}), 1 95(s, 1H, 3a-Me of rotamer **a**), 1 98(s, 2H, 3a-Me of rotamer **b**), 2 05-2 20(m, 2H, 6-H_{eq}, 9-H_{eq}), 2 47(dd, *J*=7 and 12, 0 33H, 5a-H of rotamer **a**), 2 95(dd, *J*=7 and 12, 0 67H, 5a-H of rotamer **b**), 3 82(s, 3H, CO_2Me), 6 42(d, *J*=16, 0 33H, =CHCO of rotamer **a**), 6 48(d, *J*=16, 0 67H, =CHCO of rotamer **b**), 7 13(dd, *J*=2 8 and 6, 0 67H, 3-H_{arom} of rotamer **b**), 7 22(dd, *J*=2 8 and 6, 0 33H, 3-H_{arom} of rotamer **a**), 7 52(m, 2H), 7 58(d, *J*=16, 0 33H, C_{arom}-CH= of rotamer **a**), 7 72(d, *J*=16, 0 67H, C_{arom}-CH= of rotamer **b**), 7 80(m, 1H), ^{13}C NMR($CDCl_3$) δ 20 70(3a-Me), 21 21(3a-Me), 21 45(CH_2), 21 51(CH_2), 22 00(CH_2), 25 38(CH_2), 26 44(CH_2), 27 01(CH_2), 27 51(CH_2), 44 00(C-5a), 44 99(C-5a), 51 90(CO_2*Me*), 51 99(CO_2*Me*), 69 95(C-9a), 70 28(C-9a), 110 22(C-3a), 110 41(C-3a), 121 14(CH), 123 12(CH), 128 05(CH), 128 42(CH), 130 39(CH), 130 85(CH), 131 49(CH), 131 56(CH), 131 88, 132 26, 132 59(CH), 135 35, 135 88, 138 26(CH), 139 36(CH), 152 91(C-2), 153 46(C-2), 166 02(*C*O_2Me), 166 68(*C*O_2Me), 172 58(C-5), 173 28(C-5), MS(CI) m/z 372(M^++1, 43%), 340(27), 296(33), 169(85), 151(100), Anal Calcd for $C_{20}H_{21}NO_6$ C, 64 68, H, 5 70, N, 3 77% Found C, 64 30, H, 5 71, N, 4 00%

(*E*)-(3a*R,5a*R**,9a*R**)-2'-(2,5-dioxo-3a-methyl-1,2,5,5a,6,7,8,9-octahydro-3a*H*-isobenzofuro[7a,1-*d*]oxazol-1-yl)cinnamonitrile (17):**

inseparable rotamer mixture a b=1 3, IR(KBr) ν 2250(CN), 1780(C=O)cm^{-1}, ^{1}H NMR($CDCl_3$) δ 1 00(m, 1H, 7-H_{ax}), 1 35-1 90(m, 5H, 7-H_{eq}, 8-H_2, 6-H_{ax}, 9-H_{ax}), 1 99(s, 0 75H, 3a-Me of rotamer **a**), 2 02(s, 2 25H, 3a-Me of rotamer **b**), 2 05-2 30(m, 2H, 6-H_{eq}, 9-H_{eq}), 2 40(dd, *J*=6 and 11, 0 25H, 5a-H of rotamer **a**), 2 91(dd, *J*=6 and 11, 0 75H, 5a-H of rotamer **b**), 5 94(d, *J*=16, 0 25H, =CHCN of rotamer **a**), 5 96(d, *J*=16,

0 75H, =CHCN of rotamer **b**), 7 15(m, 1H, 3-H_{arom}), 7.32(d, *J*=16, 0 25H, C_{arom}-CH= of rotamer **a**), 7 42(d, *J*=16, 0 75H, C_{arom}-CH= of rotamer **b**), 7 55(m, 2H), 7 70(m, 1H); ^{13}C NMR($CDCl_3$) δ 20 88(3a-Me), 21 19(3a-Me), 21 62(CH_2), 21 72(CH_2), 21.98(CH_2), 25 92(CH_2), 26 28(CH_2), 27 19(CH_2), 27 35(CH_2), 44 31(C-5a), 44 89(C-5a), 70.23(C-9a), 100 09(=*C*HCN), 101 61(=*C*HCN), 110 40(C-3a), 117 40(CN), 127 41(CH), 127 68(CH), 130 54(CH), 131 61(CH), 131 79(CH), 132 42(CH), 132 68(CH), 134 60, 144 17(C_{arom}-CH=), 145 44(C_{arom}-CH=), 151 2(C-2), 152 5(C-2), 172 94(C-5), MS(CI) m/z 339(M^++1, 100%), 171(38), 151(40), Anal Calcd for $C_{19}H_{18}N_2O_4$ C, 67 45, H, 5 36, N, 8 28% Found C, 67 16, H, 5 44, N, 8 28%

Methyl (*E*)-(3a*R,5a*R**,9a*R**)-2'-(2,5-dioxo-3a-methyl-1,2,5,5a,6,7,8,9-octahydro-3a*H*-isobenzofuro[7a,1-*d*]oxazol-1-yl)-2-methylcinnamate (18):**

inseparable rotamer mixture a·b=1 1; IR(KBr) ν 1805(C=O), 1765(C=O), 1710(C=O)cm^{-1}, ^1H NMR($CDCl_3$) δ 1 00(m, 0 5H), 1 08(m, 0.5H), 1 32-1 62(m, 3H), 1 65-1 85(m, 3H), 1 85-2 20(m, 2H), 1 93(s, 1 5H, 3a-Me), 1 95(s, 1 5H, 3a-Me), 2 05(d, 3H, olefin Me), 2 35(dd, *J*=7 and 12, 0.5H, 5a-H of rotamer **a**), 3 02(t, *J*=7, 0 5H, 5a-H of rotamer **b**), 3 82(s, 3H, OMe), 7 18(d, *J*=8, 0 5H, 3-H_{arom} of rotamer **b**), 7 23(d, *J*=8, 0 5H, 3-H_{arom} of rotamer **a**), 7 42-7 55(m, 3 5H, 4, 5, 6-H_{arom} and C_{arom}-CH= of rotamer **a**), 7 65(br s, 0 5H, C_{arom}-CH= of rotamer **b**), ^{13}C NMR($CDCl_3$) δ 14 14(olefin Me), 14 21(olefin Me), 20 39(3a-Me), 21 19(CH_2), 21.24(CH_2), 21 35(3a-Me), 22 10(CH_2), 24 75(CH_2), 26 59(CH_2), 26 78(CH_2), 27 64(CH_2), 43 76(C-5a), 45.16(C-5a), 52 18(OMe), 52.32(OMe), 69 79(C-9a), 70 16(C-9a), 110 06(C-3a), 110 19(C-3a), 129 45(CH), 129 80(CH), 129 84(CH), 129 90(CH), 130 77(CH), 131 27(CH), 131 34(CH), 131 56, 131 78, 132 17(CH), 132 26(CH), 132 89, 133 66(CH), 135 34(CH), 137 20, 137 44, 152 56(C-2), 153 12(C-2), 167 73(ester CO), 168 30(ester CO), 172 74(C-5), 173 36(C-5), MS(CI) m/z 386(M^++1, 73%), 354(65), 310(100), 151(43), Anal Calcd for $C_{21}H_{23}NO_6$ C, 65 44, H, 6 01, N, 3 63% Found C, 65 04, H, 5 82, N, 3 70%

Methyl (*E*)-(3a*R,5a*R**,9a*R**)-2'-(2,5-dioxo-3a-methyl-1,2,5,5a,6,7,8,9-octahydro-3a*H*-isobenzofuro[7a,1-*d*]oxazol-1-yl)-3'-methoxycinnamate, rotamer a (19a):**

less mobile on *TLC* compared to **19b** (silica gel, eluent, $CHCl_3$ AcOEt = 9 1), mp 214-5°C($CHCl_3$ - Et_2O), IR(KBr) ν 1780(C=O), 1710(C=O)cm^{-1}, ^1H NMR($CDCl_3$) δ 1 08(m, 1H, 7-H_{ax}), 1 30-1 50(m, 2H, 7-H_{eq}, 8-H_{ax}), 1 50-1 65(m, 3H, 8-H_{eq}, 6-H_{ax}, 9-H_{ax}), 1 92(s, 3H, 3a-Me), 2 00-2 10(m, 2H, 6-H_{eq}, 9-H_{eq}), 2 75(dd, *J*=7 and 12, 1H, 5a-H), 3 83(s, 3H, CO_2Me), 3 87(s, 3H, OMe), 6 42(d, *J*=16, 1H, =CHCO), 7 05(d, *J*=8, 1H, 4-H_{arom}), 7 30(d, *J*=8, 1H, 6-H_{arom}), 7 45(t, *J*=8, 1H, 5-H_{arom}), 7 63(d, *J*=16, 1H, C_{arom}-CH=), ^{13}C NMR($CDCl_3$) δ 20 81(3a-Me), 21 48(C-8), 21 53(C-7), 25 18(C-6), 25 73(C-9), 45 03(C-5a), 51 93(CO_2*Me*), 56 05(OMe), 70 93(C-9a), 110 49(C-3a), 113 62(C_{arom}-4), 119 84(C_{arom}-6), 121 74(C_{arom}-2), 122 60(=*C*HCO), 130 95(C_{arom}-5), 136 79(C_{arom}-1), 139 12(C_{arom}-*C*H=), 153 66(C-2), 157 59(C_{arom}-3), 166 23(*C*O_2Me), 172 98(C-5), MS(CI) m/z 402(M^++1, 100%), 326(70), Anal Calcd for $C_{21}H_{23}NO_7$ C, 62 84, H, 5 78, N, 3.49% Found C, 62 56, H, 5 72, N, 3 51%

Methyl (*E*)-(3a*R,5a*R**,9a*R**)-2'-(2,5-dioxo-3a-methyl-1,2,5,5a,6,7,8,9-octahydro-3a*H*-isobenzofuro[7a,1-*d*]oxazol-1-yl)-3'-methoxycinnamate, rotamer b (19b):**

mp 199-201°C($CHCl_3$-Et_2O), IR(KBr) ν 1780(C=O), 1710(C=O)cm^{-1}; ^1H NMR($CDCl_3$) δ 1 05(m, 1H, 7-H_{ax}), 1 30-1 80(m, 5H, 7-H_{eq}, 8-H_2, 6-H_{ax}, 9-H_{ax}), 1 96(s, 3H, 3a-Me), 2 00-2 10(m, 2H, 6-H_{eq}, 9-H_{eq}), 2 68(dd, *J*=7 and 11, 1H, 5a-H), 3 79(s, 3H, OMe), 3 81(s, 3H, CO_2Me), 6 45(d, *J*=16, 1H, =CHCO), 7 05(dd, *J*=1 and 8, 1H, 4-H_{arom}), 7 33(dd, *J*=1 and 8, 1H, 6-H_{arom}), 7 45(t, *J*=8, 1H, 5-H_{arom}), 7 74(d,

J=16, 1H, C_{arom}-CH=), ^{13}C NMR($CDCl_3$) δ 20 51(3a-Me), 21 41(C-8), 21 54(C-7), 25 57(C-6), 28.02(C-9), 43.49(C-5a), 51 75(CO_2Me), 55 33(OMe), 70 36(C-9a), 110 49(C-3a), 113 57(C_{arom}-4), 119 46(C_{arom}-6), 121 25(=*C*HCO), 121 53(C_{arom}-2), 131 37(C_{arom}-5), 137 14(C_{arom}-1), 140 40(C_{arom}-*C*H=), 153 54(C-2), 157 75(C_{arom}-3), 167 16(CO_2Me), 174.28(C-5), MS(CI) m/z 402(M^++1, 100%), 326(20), Anal Calcd for $C_{21}H_{23}NO_7$· C, 62.84; H, 5.78, N, 3 49% Found. C, 62 62, H, 5 72, N, 3.44%

(1*R,2*R**,8*R**,9*S**)-5-Aza-3,14-dioxa-4,15-dioxo-8-methoxycarbonylmethyl-2-methyl-benzo[6,7]tetracyclo[7.4.0.2.^{2,9}0^{1,5}]pentadecane (22):**

IR(KBr) ν 1780(C=O), 1735(C=O)cm^{-1}, ^{1}H NMR($CDCl_3$) δ 1 20(m, 1H, 11-H_{ax}), 1 28-1 40(m, 2H, 13-H_{ax}, 10-H_{ax}) 1.50-1.64(m, 3H, 11-H_{eq}, 12-H_2), 1 80-1 95(m, 2H, 13-H_{eq}, 10-H_{eq}), 1 92(s, 3H, 2-Me), 2 85(m, 1H, one of the 8-CH_2), 3 37(m, 1H, 8-H), 3 42(m, 1H, one of the 8-CH_2), 3 68(s, 3H, CO_2Me), 7.20(d,J=8, 1H, 3'-H), 7 34(t, J=8, 1H, 4'-H), 7 39(t, J=8, 1H, 5'-H), 7 44(d, J=8, 1H, 6'-H), ^{13}C NMR($CDCl_3$) δ 16 87(C-12), 17 20(C-11), 21 26(2-Me), 24 46(C-10), 25 89(C-13), 30 82(8-CH_2), 38 76(C-8), 52 17(OMe), 55 29(C-9), 69 08(C-1), 108 53(C-2), 125 24(C-3'), 125 68(C-6'), 128 02(C-4'), 128 33(C-5'), 132 21(C-6 or 7), 134 37(C-6 or 7), 151 78(C-4), 171 59(ester C=O), 176 29(C-15), MS(CI) m/z 372(M^++1, 100%), Anal Calcd for $C_{20}H_{21}NO_6$ C, 64 68, H, 5 70, N, 3 77% Found C, 65 01, H, 5 80, N, 3 88%

(1*R,2*R**,8*R**,9*S**)-5-Aza-3,14-dioxa-4,15-dioxo-8-cyanomethyl-2-methyl-benzo[6,7]tetracyclo[7.4.0.2.^{2,9}0^{1,5}]pentadecane (23):**

IR(KBr) ν 1785(C=O)cm^{-1}, ^{1}H NMR($CDCl_3$) δ 1 25(m, 1H), 1 37(m, 1H), 1 50-1 70(m, 4H), 1 82(m, 1H), 1 90(m, 1H), 1 93(s, 3H, 2-Me), 3 03(dd, J=9 and 17, one of the 8-CH_2), 3 20(dd, J=4 and 9, 8-H), 3 40(dd, J=4 and 17, one of the 8-CH_2), 7 42-7 55(m, 4H), ^{13}C NMR(DMSO-d_6) δ 14 85(8-CH_2), 17 19(C-12), 17 59(C-11), 20 80(2-Me), 24 71(C-10), 25 39(C-13), 37 64(C-8), 54 17(C-9), 67 94(C-1), 108 96(C-2), 119 58(CN), 124 57(CH), 126 08(CH), 127 40(CH), 128 43(CH), 130 09(C-6), 133 91(C-7), 150 82(C-4), 176 22(C-15), MS(CI) m/z 339(M^++1, 100%), Anal Calcd for $C_{19}H_{18}N_2O_4$ C, 67.45, H, 5 36, N, 8 28% Found C, 67 41, H, 5 36, N, 8 18%

(1*R,2*R**,8*R**,9*S**)-5-Aza-3,14-dioxa-4,15-dioxo-6'-methoxy-8-methoxycarbonylmethyl-2-methyl-benzo[6,7]tetracyclo[7.4.0.2.^{2,9}0^{1,5}]pentadecane (24):**

IR(KBr) ν 1780(C=O), 1730(C=O)cm^{-1}, ^{1}H NMR($CDCl_3$) δ 1.05-1 20(m, 2H, 11-H_{ax}, 10-H_{ax}), 1 25-1 35(m, 1H, 13-H_{ax}) 1 56-1 63(m, 3H, 11-H_{eq}, 12-H_2), 1 83(m, 1H, 10-H_{eq}), 1 95(s, 3H, 2-Me), 1 90-2 00(m, 1H, 13-H_{eq}), 2 81(dd, J=11 and 16, 1H, one of the 8-CH_2), 3 32(dd, J=2 and 11, 1H, 8-H), 3 42(dd, J=2 and 16, 1H, one of the 8-CH_2), 3 66(s, 3H, CO_2Me), 3 90(s, 3H, OMe), 6 91(d, J=8, 1H, 3'-H), 6 97(d, J=8, 1H, 5'-H), 7 32(t, J=8, 1H, 4'-H), ^{13}C NMR($CDCl_3$) δ 16 20(C-12), 16 75(C-11), 21 40(2-Me), 23 68(C-10), 25 38(C-13), 30 83(8-CH_2), 39 25(C-8), 52 21(ester OMe), 55 76(C-9), 56 20(OMe), 69 81(C-1), 108 81(C-2), 111 67(C-5'), 117 10(C-3'), 122 95(C-6), 129 41(C-4'), 134 82(C-7), 151 63(C-4), 155 69(C-6'), 171 63(ester C=O), 176 32(C-15), MS(CI) m/z 402(M^++1, 100%), 358(47), 286(26), Anal Calcd for $C_{21}H_{23}NO_7$ C, 62 84, H, 5 78; N, 3 49% Found C, 62 62, H, 5 65, N, 3 50%

(1*R,2*R**,8*R**,9*S**)-5-Aza-6'-chloro-3,14-dioxa-4,15-dioxo-8-methoxycarbonylmethyl-2-methyl-benzo[6,7]tetracyclo[7.4.0.2.^{2,9}0^{1,5}]pentadecane (25):**

IR(KBr) ν 1770(C=O), 1730(C=O)cm^{-1}, ^{1}H NMR($CDCl_3$) δ 1 05-1 38(m, 3H, 11-H_{ax}, 13-H_{ax}, 10-H_{ax}) 1 50-1 70(m, 3H, 11-H_{eq}, 12-H_2), 1 83-1 93(m, 1H, 10-H_{eq}), 1 96(s, 3H, 2-Me), 1 95-2 08(m, 1H, 13-H_{eq}), 2 80(dd, J=11 and 16, 1H, one of the 8-CH_2), 3 32(dd, J=2 4 and 11, 1H, 8-H), 3 47(dd, J=2 4 and

16, 1H, one of the 8-CH_2), 3 67(s, 3H, CO_2Me), 7 15(d, J=8, 1H, 3'-H), 7 33(t, J=8, 1H, 4'-H), 7 46(d, J=8, 1H, 5'-H), ^{13}C NMR($CDCl_3$) δ 15 63(C-12), 16 14(C-11), 20 97(2-Me), 23 22(C-10), 25 21(C-13), 30.31(8-CH_2), 39.23(C-8), 52 16(OMe), 55.48(C-9), 69 84(C-1), 109 08(C-2), 124 16(C-5'), 129 59(C-3' or 4'), 129 75(C-3' or 4'), 132 62(C-6'), 133 18(C-6), 135 95(C-7), 151 45(C-4), 171 81(ester C=O), 176 33(C-15), MS(CI) m/z 406(M^++1, 100%), 408(M^++3, 36), Anal Calcd for $C_{20}H_{20}ClNO_6$ C, 59 19, H, 4 97, N, 3.45% Found: C, 58 87; H, 4 66; N, 3 36%

(1*R,2*R**,8*R**,9*S**)-5-Aza-2,6'-dimethyl-3,14-dioxa-4,15-dioxo-8-methoxycarbonylmethyl-benzo[6,7]tetracyclo[7.4.0.0.2.^{2,9}0^{1,5}]pentadecane (26):**
IR(KBr) ν 1765(C=O), 1735(C=O)cm^{-1}; ^1H NMR($CDCl_3$) δ 1 10-1 38(m, 3H, 11-H_{ax}, 13-H_{ax}, 10-H_{ax}) 1 50-1 65(m, 3H, 11-H_{eq}, 12-H_2), 1 85(m, 2H, 10-H_{eq}, 13-H_{eq}), 1 95(s, 3H, 2-Me), 2 37(s, 3H, 6'-Me), 2 80(dd, J=11 and 16, 1H, one of the 8-CH_2), 3 32(dd, J=2 and 11, 1H, 8-H), 3 44(dd, J=2 and 16, 1H, one of the 8-CH_2), 3 65(s, 3H, CO_2Me), 7 05(m, 1H, 4'-H), 7 25(m, 2H, 3' and 5'-H), ^{13}C NMR($CDCl_3$) δ 15 72(C-12), 16 19(C-11), 16.82(6'-Me), 20 99(2-Me), 23 08(C-10), 25 19(C-13), 30 33(8-CH_2), 38 93(C-8), 51 98(OMe), 55 30(C-9), 69 84(C-1), 108 90(C-2), 123 10(CH), 128 61(CH), 130 25(CH), 133 09, 133 59, 136 44, 152 09(C-4), 172 10(ester C=O), 176 69(C-15), MS(CI) m/z 386(M^++1, 100%), 354(31), Anal Calcd for $C_{21}H_{23}NO_6$ C, 65 44, H, 6 01, N, 3 63% Found C, 65 65, H, 6 01, N, 3 69%

General Procedure for the Preparation of Octahydroacridines 27 - 29 To a stirred solution of an appropriate tandem adduct (2 mmol) in MeOH (10 mL) was added 28% MeONa in MeOH (0 39 g, 2 mmol) The mixture was refluxed for 3 h, then MeOH was removed under reduced pressure The residue was poured into 0 1*N* HCl (20 mL), and extracted with Et_2O (20 mL x 3), washed with water (10 mL), then dried over anhydrous $MgSO_4$ After removal of Et_2O, the residue was recrystallized from *n*-hexane - Et_2O or $CHCl_3$ - Et_2O to afford the octahydroacridines **27 - 29**

(4a*R,9*R**,9a*S**)-4a-Acetyl-9a-methoxycarbonyl-9-methoxycarbonylmethyl-1,2,3,4,4a,9,9a,10-octahydroacridine (27):**
Yield 95%, mp 148-9°C ($CHCl_3$ - Et_2O), IR(KBr) ν 3400(NH), 1735(C=O)cm^{-1}, ^1H NMR($CDCl_3$) δ 1 16(dt, J=4 5 and 13 5, 1H, 1-H_{ax}), 1 47-1 57(m, 3H, 2-H_{ax}, 3-H_{ax}, 4-H_{ax}), 1 62(m, 1H, 3-H_{eq}) 1 72(m, 1H, 1-H_{eq}), 1 93(m, 1H, 2-H_{eq}), 2 17(m, 1H, 4-H_{eq}), 2 20(s, 3H, Ac), 2 60(m, 2H, 9-CH_2), 3 70(s, 3H, CO_2Me), 3 76(s, 3H, CO_2Me), 3 85(br s, 1H, NH), 4 05(m, 1H, 9-H), 6 57(d, J=8, 1H, 5-H), 6 70(t, J=8, 1H, 7-H), 6 93(d, J=8, 1H, 8-H), 7 06(t, J=8, 1H, 6-H), ^{13}C NMR($CDCl_3$) δ 19 62(C-3), 21 14(C-2), 25 60(C-1), 27 76(Ac), 31 66(C-4), 35 99(9-CH_2), 37 64(C-9), 48 45(C-9a), 51 94(OMe), 52 16(OMe), 65 12(C-4a), 113 11(C-5), 117 98(C-7), 120 92(C-10a), 127 32(C-8), 127 63(C-6), 140 95(C-8a), 173 61(CO_2Me), 173 99(CO_2Me), 210 50(Ac), MS(CI) m/z 360(M^++1, 62%), 328(100), 316(86), Anal Calcd for $C_{20}H_{25}NO_5$ C, 66 84, H, 7 01, N, 3 90% Found C, 66 96, H, 6 93, N, 3 86%

(4a*R,9*R**,9a*S**)-(4a-Acetyl-5-methoxy-9a-methoxycarbonyl-9-methoxycarbonylmethyl-1,2,3,4,4a,9,9a,10-octahydroacridine (28):**
Yield 85%, mp 127-8°C (Et_2O - *n*-hexane), IR(KBr) ν 3400(NH), 1735(C=O), 1700(C=O)cm^{-1}, ^1H NMR($CDCl_3$) δ 1 13(dt, J=4 5 and 13 5, 1H, 1-H_{ax}), 1 45-1 80(m, 5H, 1-H_{eq}, 2-H_{ax}, 3-H_2, 4-H_{ax}), 1 80-2 00(m, 1H, 2-H_{eq}), 2 15-2 25(m, 1H, 4-H_{eq}), 2 19(s, 3H, Ac), 2 60(m, 2H, 9-CH_2), 3 71(s, 3H, CO_2Me), 3 77(s, 3H, CO_2Me), 3 87(s, 3H, OMe), 4 05(dd, J=4 and 7, 1H, 9-H), 4 42(br s, 1H, NH), 6 64(m, 3H, 6, 7, 8-H), ^{13}C NMR($CDCl_3$) δ 19 30(C-3), 20 81(C-2), 25 35(C-1), 27 17(Ac), 31 28(C-4), 35 74(9-CH_2), 37 39(C-9), 48 05(C-9a), 51 68(ester OMe), 51 91(ester OMe), 55 38(OMe), 64 63(C-4a), 107 86(C-6),

116 55(C-7), 119 38(C-8), 120 91(C-10a), 130 95(C-8a), 145.42(C-5), 174 15(CO_2Me), 174 66(CO_2Me), 211 33(Ac), MS(CI) m/z 390(M^++1, 85%), 358(63), 346(100), Anal Calcd for $C_{21}H_{27}NO_6$ C, 64 77, H, 6 99, N, 3 60% Found C, 64.58, H, 7.03, N, 3.63%

(4a*R,9*R**,9a*S**)-4a-Acetyl-5-chloro-9a-methoxycarbonyl-9-methoxycarbonylmethyl-1,2,3,4,4a,9,9a,10-octahydroacridine (29):**
Yield 90%; mp 140-1°C ($CHCl_3$ - Et_2O), IR(KBr) ν 3320(NH), 1740(C=O), 1720(C=O), 1695cm^{-1}, ^1H NMR($CDCl_3$) δ 1 10(dt, J=4.5 and 14, 1H, 1-H_{ax}), 1 45-1 80(m, 5H, 1-H_{eq}, 2-H_{ax}, 3-H_2, 4-H_{ax}), 1 85-2 05(m, 1H, 2-H_{eq}), 2.19(s, 3H, Ac), 2.20-2.35(m, 1H, 4-H_{eq}), 2 60(d, J=5, 2H, 9-CH_2), 3 72(s, 3H, CO_2Me), 3.77(s, 3H, CO_2Me), 4.04(t, J=5, 1H, 9-H), 4 53(br s, 1H, NH), 6 63(t, J=8, 1H, 7-H), 6 86(d, J=8, 1H, 8-H), 7 18(d, J=8, 1H, 6-H), ^{13}C NMR($CDCl_3$) δ 19 15(C-3), 20 64(C-2), 25 29(C-1), 27 13(Ac), 31 37(C-4), 35 80(9-CH_2), 37 52(C-9), 48 03(C-9a), 51 82(OMe), 52 00(OMe), 65 09(C-4a), 117 58(C-5), 117 72(C-7), 123 01(C-10a), 126 07(C-6), 127 63(C-8), 137 33(C-8a), 173 89(CO_2Me), 174 21(CO_2Me), 210 96(Ac), MS(CI) m/z 394(M^++1, 33%), 362(100), 350(56), Anal Calcd for $C_{20}H_{24}ClNO_5$ C, 60 99, H, 6 14, N, 3 56%. Found C, 60 96, H, 5 98, N, 3 66%

Determination of Barriers to Rotation for Compound 16 by the saturation transfer method For experimental details, see our previous paper [8] We obtained following rate constants for rotation at 25°C The equilibrium constant K was 0 48 in favor of rotamer **16b**

T_{1Aeff} (s)	0 97	M_A / M_{0A}	0 58	k_A (s^{-1})	0 76
T_{1Beff} (s)	0 98	M_B / M_{0B}	0 70	k_B (s^{-1})	0 45

Determination of Barriers to Rotation for Compounds 19a and 19b Compound **19a** or **19b** (30 mg) was separately mixed in diphenylether (0 5 mL) and the solution was placed in a boiling toluene (111 °C) bath After an interval, a small portion of the solution was taken into a NMR sample tube and dissolved in $CDCl_3$ The decrease in the starting material and increase in the corresponding rotamer were determined by integration of the respective NMR signals The ratio of **19a** and **19b** was also checked by HPLC (column Cosmosil 10C18-P, 4 6 mm x 25 cm, Mobile phase MeOH McIlvaine buffer pH 2 2 = 6 4, flow rate 2mL/min , detected at 254 nm Retention time of **19a** = 3 6 min **19b** = 4 0 min) The equilibrium constant K was 0 25 in favor of **19b**, obtained after 12 h at 111 °C The rate constants were obtained by assuming a reversible first-order process
k_A (s^{-1}) = 1 4 x 10^{-4} (111 °C), k_B (s^{-1}) = 3 5 x 10^{-5} (111 °C)

X-Ray Crystallographic Analysis for Compound 24. Crystal data $C_{21}H_{23}NO_7$, M = 401 42, monoclinic, a = 16 217(8), b = 22 70(1), c = 10 776(5) Å, β = 105 65(4)°, V = 3820(3)Å^3, space group $P21/a$, Z = 4, Dc = 1 39 gcm^{-3}, R = 0 068 Full crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U K

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9 The tricyclic compounds **16-21** possess both chiral centers and chiral axis Since our starting material **14** is racemic, the stereochemical relation should be (3a*R**, 5a*R**, 9a*R**), and only 3a*S*-form is shown in Scheme 3 As for the chiral axis of the benzene ring, it should be (*R**) if olefinic moiety precedes X For the expediency of discussion, the rotamers are indicated by adding subscripts **a** and **b** to their compound number Thus **16** indicates a mixture of rotamers and **16a** indicates one of the rotamers whose olefinic moiety is oriented to site A as shown in Scheme 1

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14 It should be noted that the free energy of activation higher than *ca* 23 kcal/mol is required for the isolation of the each rotamer at room temperature See reference 2, pp 5

15 We thank one of the referees for suggesting the possibility of DBU-catalyzed isomerization

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