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[3+2] Dipolar Cycloaddition of 1-Pyrroline 1-Oxide with 2-Aryl-3-butenoates. Application to Prepare Bicyclic Heterocyclic Compounds

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Five- and six-membered ring systems containing a nitrogen atom at the bridgehead position were prepared *via* [3+2] dipolar cycloaddition of 1-pyrroline 1-oxide (**5**) with 2-aryl-3-butenoates. Cycloaddition of **5** with methyl 4,4-dichloro-2-[4-(tosyloxy)phenyl]-3-butenoate (**4**) gave 3(and 2)-dichloromethyl-2(and 3)-methoxycarbonyl-2(and 3)-[4-(tosyloxy)phenyl]-2,3,3a,4,5,6-hexahydropyrrolo[1,2-*b*]isoxazole (**6** and **7**) in a ratio of 52:10. Compound **6** was converted to 1-aza-3-*r*-hydroxy-4-*c*-methyl-3-*t*-[4-(tosyloxy)phenyl]bicyclo[3.3.0]octan-2-one (**12**) by treatment with zinc in aqueous acetic acid in one step or *via* the 4-chloromethyl analog of **12** (*i.e.*, **11**). On the other hand, cycloaddition of **5** with methyl 2-phenyl-3-butenoate (**15**) afforded methyl 2,3,3aα,4,5,6-hexahydropyrrolo[1,2-*b*]isoxazol-2α-yl phenyl acetate (**16**) and 2-methoxycarbonyl-3-methyl-2-phenyl-2,3,3a,4,5,6-hexahydropyrrolo[1,2-*b*]isoxazole (**17**) and its regioisomer (**18**) in a ratio of 17:31:32. Treatment of **16** with zinc in aqueous acetic acid furnished 1-aza-4β-hydroxy-3α-phenyl-5aα*H*-bicyclo[4.3.0]nonan-2-one (**20**).

Keywords——1,3-dipolar cycloaddition; cyclic nitrone; 2-aryl-3-butenoate; hexahydropyrrolo-[1,2-*b*]isoxazole; intramolecular cyclization; 1-azabicyclo[3.3.0]octan-2-one; 1-azabicyclo[4.3.0]-nonan-2-one

1,3-Dipolar cycloaddition reactions of nitrones with nonsymmetric dipolarophiles, *i.e.*, monosubstituted alkenes, occur regioselectively (or regiospecifically) to afford 5-substituted isoxazolidines.[1] This rule has been explained in terms of frontier orbital considerations.[2] Thus, cycloaddition of 1-pyrroline 1-oxide with methyl 3-butenoate has been found to proceed regiospecifically and has been successfully utilized in the total synthesis of cocaine.[3] In the course of our studies of the synthesis of indolizidine and pyrrolizidine alkaloids *via* [3+2] dipolar cycloaddition of nitrones,[4] we were interested in the cycloaddition reaction between 1-pyrroline 1-oxide and 2-aryl-3-butenoates since it appeared to represent a new entry into the fused five- and six-membered ring systems containing nitrogen at the bridgehead position. In this paper we describe the results of this work.

First, we chose the 2-aryl-4,4-dichloro-3-butenoate (**3**) as the dipolarophile in an attempt to obtain the 2,3,3-trisubstituted pyrroloisoxazolidine derivative (**9**), which was expected to provide a potential intermediate for the synthesis of the indolizidinone (**21**), recognized as a versatile precursor to (±)-ipalbidine (**22**) (see below). For the synthesis of the target dipolarophile, Friedel-Crafts reaction of phenol with γ,γ,γ-trichlorocrotonic acid (**1**) was carried out to give 4,4-dichloro-2-(4-hydroxyphenyl)-3-butenoic acid (**2**) in 72% yield, and this was subsequently converted into the tosyl ester (**4**) by esterification followed by tosylation (Chart 1).

Cycloaddition was accomplished by the reaction of the cyclic nitrone (**5**) with **4** in refluxing toluene for 4 h to give the 2,2,3- and 2,3,3-trisubstituted isoxazolidines (**6** and **7**) in 52 and 10% yields, respectively, based on the recovered 2-butenoate (**8**) (47%). In this reaction, formation of **9** and/or **10** was not observed. From these results, initial double bond

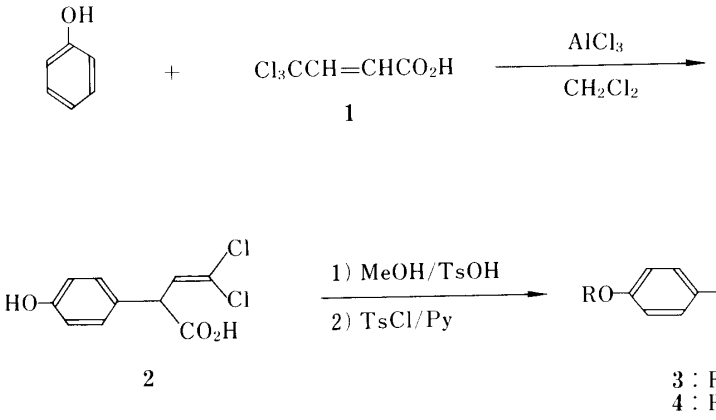

Chart 1

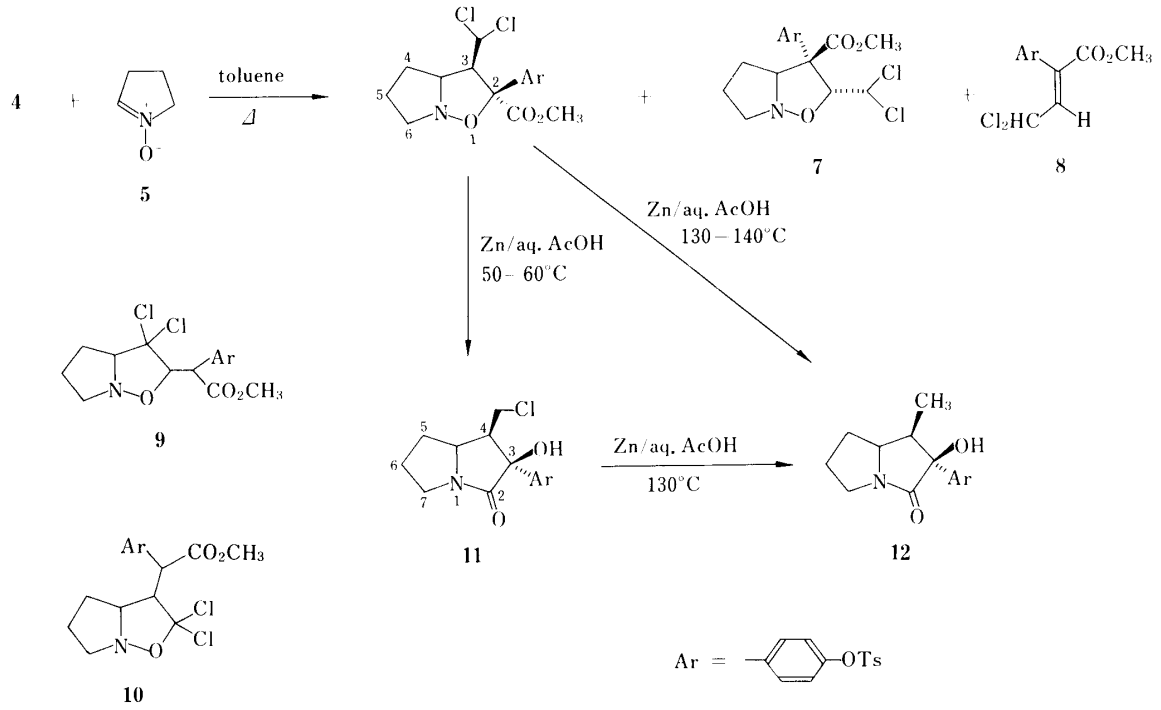

Chart 2

migration of **4** occurring prior to cycloaddition to produce the γ,γ-dichlorocrotonate (**8**) was postulated. Double bond migration of **4** to **8** may have occurred under the basic conditions due to the nitrone used in the reaction. In fact, although no isomerization was observed on prolonged heating of **4** at reflux in toluene without the catalyst, **4** was completely isomerized to **8** when heated in toluene with triethylamine. The *E* stereochemistry of the double bond in **8** was supported by the ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectrum. It showed a doublet due to the vinyl proton at δ 7.13, indicating that the vinyl proton is situated *cis* to the methoxycarbonyl group rather than to the phenyl group.[5] Thus, the C-2/C-3 *trans* stereochemistry for the cycloadducts (**6** and **7**) would arise from the *E* geometry of **8**. While crotonates are known to undergo cycloaddition with nitrones to afford β-oxa esters,[6] the preponderant formation of the α-oxa ester (**6**) over the β-oxa ester (**7**) was observed in the present case with the 2-arylcrotonate (**8**). The reversal of regiochemical preference with **8** can be presumed to involve both steric and electronic factors.[7]

When treated with zinc in 50% aqueous acetic acid (50—60 °C, 48 h), the isoxazolidine (**6**) underwent reductive N–O bond cleavage followed by *in situ* cyclization to afford the

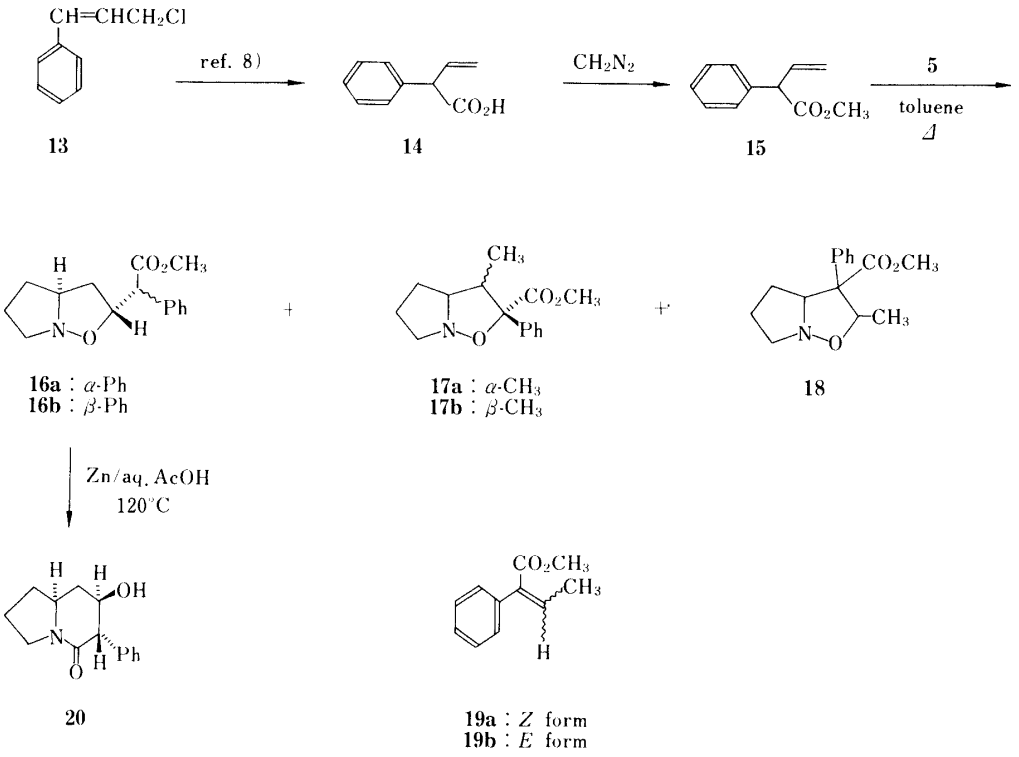

Chart 3

Chart 4

pyrrolizidine (**11**) in 86% yield. Further reductive treatment of **11** with zinc in 90% aqueous acetic acid gave the dechlorinated product (**12**) in 92% yield. Alternatively, **12** was directly led from **6** in 87% yield by treatment with zinc in 90% aqueous acetic acid at higher temperature (130—140 °C) and prolonged reaction time.

Next we chose the 2-phenyl-3-butenoate (**15**) as the dipolarophile; it was prepared by Grignard treatment of cinnamyl chloride (**13**) according to the literature procedure[8] followed by esterification with diazomethane. Cycloaddition of the nitrone (**5**) and **15** was carried out in refluxing toluene to give three adducts, **16**, **17**, and **18**, in 17, 31, and 32% yields, respectively (Chart 3).

This result was somewhat different from that observed above in the nitrone cycloaddition of **4**. Namely, after isomerization of **15** to methyl 2-phenylcrotonate (**19**), cycloaddition occurred, providing almost equal amounts of the α- and β-oxa esters (**17** and **18**). The former product (**17**) actually consisted of two diastereomers (total isolated yield: 31%) which were separated by preparative thin layer chromatography (TLC) in a ratio of 16 : 15. These isomers were readily distinguishable on the basis their ^{1}H-NMR and ^{13}C-nuclear magnetic resonance (^{13}C-NMR) spectra (see Experimental) and were considered to have the structure **17a** and **17b** resulting from the (*Z*)- and (*E*)-crotonates (**19a** and **19b**), respectively. However the assignment of the individual products was uncertain. Furthermore, a part of the starting ester

(**15**) was, without isomerization, subjected to direct cycloaddition to give **16**, which was apparently a diastereomeric mixture (6:5 ratio by ^{1}H-NMR) of **16a** and **16b**. The *trans* stereochemistry of **16** between H-2 and H-3a was tentatively assigned on the basis of the concept of thermodynamic preference for an *exo* transition state involving the nonconjugated monosubstituted olefin as the dipolarophile.[9]

Partial isomerization of **15** to the (*Z*)/(*E*)-crotonates (**19a** and **19b**) during the cycloaddition under basic conditions was confirmed by the following observation: a solution of **15** in toluene in the presence of triethylamine was heated at reflux for 4 h to produce unchanged **15** and the *Z* and *E* isomers (**19a** and **19b**). These isomers (**19a** and **19b**) were clearly distinguishable on the basis of the ^{1}H-NMR signals due to the methyl groups, which appeared as doublets at δ 2.05 and 1.74, respectively.[10] ^{1}H-NMR analysis of compounds **15**, **19a**, and **19b** arising from the isomerization reaction yielded a ratio of 45:37:18. The same ratio was also obtained by gas-liquid chromatographic (GLC) analysis.

Reductive treatment of **16** (6:5 diastereomeric mixture) with zinc in 90% aqueous acetic acid at 120 °C provided indolizidine (**20**) in 84% yield. The *trans* diaxial relationship at H-3/H-4 in **20** was assigned on the basis of the ^{1}H-NMR spectrum showing the H-3 signal (δ 3.36) as a doublet with the coupling constant of 9.8 Hz. The product **20** possesses the equivalent functionality on the indolizidine ring system to that possessed by the indolizidinone (**21**), which has been utilized as a key intermediate for the synthesis of ipalbidine (**22**).[11]

In the above results it may be noted that [3+2] dipolar cycloaddition reaction of trisubstituted olefins with a "cyclic" nitrone, no example of which has previously appeared in the literature, smoothly proceeded to generate both the thermodynamically and kinetically controlled cycloadducts.

Experimental

Melting points were determined by using a Yanagimoto micro apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 215 spectrophotometer. ^{1}H-NMR spectra were determined at 270 MHz on a JEOL JNM-FX 270 instrument. ^{13}C-NMR spectra were obtained with the JNM-FX 270 instrument at 67.8 MHz. Tetramethylsilane was used as an internal standard. Mass spectra (MS) were taken with a JEOL JMS-D 300 mass spectrometer and a Hitachi M-80 (equipped with a Hitachi M-003 data processing system) double-focusing mass spectrometer at an ionizing potential of 70 eV. GLC was performed on a Shimadzu GC-7AG instrument with a flame-ionization detector and a 1 m column of 2% OV-101 on Chromosorb G (AW-DMCS, 80—100 mesh). TLC was run on Merck precoated Silica gel 60-F 254 plates. Merck Silica gel 60 (230—400 mesh) was used for column chromatography.

4,4-Dichloro-2-(4-hydroxyphenyl)-3-butenoic Acid (2)——Powdered $AlCl_3$ (68 g, 0.51 mol) was added in small portions to a stirred, ice-cooled mixture of **1**[12] (30.0 g, 0.158 mol) and phenol (17.9 g, 0.190 mol) in dry dichloromethane (100 ml) during a period of 20 min. After being stirred under ice cooling for another 30 min, the mixture was heated at reflux for 30 min and poured into ice-water (500 ml) containing conc. HCl (50 ml). The product was extracted with ether and the ethereal layer was washed with water and dried ($MgSO_4$). The crude product obtained by evaporation of the solvent was purified by chromatography on a silica gel column with ether–hexane (1:1) to give colorless crystals, which were recrystallized from ether–hexane to give **2** (28.0 g, 72%) as colorless needles, mp 168—169.5 °C. IR ν_{max}^{KBr} cm^{-1}: 3200, 1700, 1615. ^{1}H-NMR (CD_3OD) δ: 4.46 (1H, d, J=9.1 Hz, ArCH), 6.44 (1H, d, J=9.1 Hz, Cl_2C=CH), 6.74 (2H, A part of AB q, J=8.3 Hz, ArH-3 and ArH-5), 7.11 (2H, B part of AB q, J=8.3 Hz, ArH-2 and ArH-6). ^{13}C-NMR (CD_3OD) δ: 52.3 (d), 116.5 (d), 122.6 (s), 129.1 (s), 129.6 (d), 129.8 (d), 158.0 (s), 174.2 (s). MS *m/z*: 246 (M^+), 201 (base). *Anal.* Calcd for $C_{10}H_8Cl_2O_3$: C, 48.61; H, 3.26. Found: C, 48.61; H, 3.17.

Methyl 4,4-Dichloro-2-(4-hydroxyphenyl)-3-butenoate (3)——A solution of **2** (15.5 g, 62.7 mmol) in methanol (150 ml) containing *p*-toluenesulfonic acid (3.0 g) was refluxed for 3 h. After evaporation of the solvent, the residual oil was dissolved in benzene and the benzene solution was washed with water and saturated aqueous $NaHCO_3$, then dried ($MgSO_4$). Evaporation of the solvent left an oil, which was distilled under reduced pressure to give **3** (15.82 g, 97%) as a colorless oil, bp 133—135 °C (0.05 mmHg). IR ν_{max}^{neat} cm^{-1}: 3400, 1720. ^{1}H-NMR ($CDCl_3$) δ: 3.72 (3H, s, CH_3), 4.57 (1H, d, J=9.1 Hz, ArCH), 5.53 (1H, br s, OH), 6.39 (1H, d, J=9.1 Hz, Cl_2C=CH), 6.79 (2H, A part of AB q, J=8.3 Hz, ArH-3 and ArH-5), 7.14 (2H, B part of AB q, J=8.3 Hz, ArH-2 and ArH-6). ^{13}C-NMR ($CDCl_3$) δ: 51.1 (q or d), 52.8 (d or q), 116.0 (d), 123.0 (s), 127.2 (d), 128.6 (s), 129.1 (d), 155.5 (s), 171.9 (s). MS *m/z*: 260 (M^+),

201 (base). High-resolution MS *m/z*: Calcd for $C_{11}H_{10}Cl_2O_3$ (M^+) 260.0007. Found 260.0027.

Methyl 4,4-Dichloro-2-[4-(*p*-toluenesulfonyloxy)phenyl]-3-butenoate (4)——*p*-Toluenesulfonyl chloride (1.60 g, 8.39 mmol) was added in small portions to a stirred, ice-cooled solution of **3** (1.50 g, 5.74 mmol) in pyridine (10 ml), and the mixture was stirred at 0—5 °C for 3 h. The mixture was poured into a flask containing ice-water (50 ml) and extracted with benzene. The extract was washed successively with 5% NaOH, water, and 10% HCl, then dried ($MgSO_4$). After removal of the solvent by evaporation, the residue was purified by column chromatography on silica gel with benzene–ethyl acetate (95 : 5) to give **4** (2.16 g, 90%) as colorless crystals, mp 50—51 °C (hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1615 (sh), 1370, 1160. ^{1}H-NMR ($CDCl_3$) δ: 2.46 (3H, s, $ArCH_3$), 3.71 (3H, s, OCH_3), 4.60 (1H, d, J=9.2 Hz, ArCH), 6.36 (1H, d, J=9.2 Hz, $Cl_2C=CH$), 6.98 (2H, A part of AB q, J=8.5 Hz, ArH-3 and ArH-5), 7.21 (2H, B part of AB q, J=8.5 Hz, ArH-2 and ArH-6), 7.33 (2H, A part of AB q, J=8.3 Hz, ArH-3′ and ArH-5′), 7.71 (2H, B part of AB q, J=8.3 Hz, ArH-2′ and ArH-6′). ^{13}C-NMR ($CDCl_3$) δ: 21.7 (q), 51.1 (q), 52.8 (d), 122.9 (d), 123.6 (s), 126.5 (d), 128.5 (d), 129.1 (d), 129.8 (d), 132.4 (s), 135.3 (s), 145.5 (s), 149.1 (s), 170.7 (s). MS *m/z*: 414 (M^+), 91 (base). *Anal.* Calcd for $C_{18}H_{16}Cl_2O_5S$: C, 52.06; H, 3.88. Found: C, 52.06; H, 3.83.

Reaction of the Tosyl Ester (4) with 1-Pyrroline 1-Oxide (5)——A mixture of **4** (12.7 g, 30.6 mmol) and **5** (2.6 g, 30.5 mmol) in toluene (40 ml) was heated under reflux for 4 h. Evaporation of the solvent under reduced pressure left a solid, which was subjected to column chromatography on silica gel with benzene–diisopropyl ether (20 : 1). The first fraction contained methyl (*E*)-4,4-dichloro-2-[4-(*p*-toluenesulfonyloxy)phenyl]-2-butenoate (**8**) (6.0 g, 47%) as colorless prisms, mp 110—111 °C (benzene–hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710, 1615, 1370, 1150. ^{1}H-NMR ($CDCl_3$) δ: 2.47 (3H, s, $ArCH_3$), 3.80 (3H, s, OCH_3), 5.93 (1H, d, J=10.2 Hz, Cl_2CH), 7.09 (2H, A part of AB q, J=8.5 Hz, ArH-3 and ArH-5), 7.13 (1H, d, J=10.2 Hz, $=CHCHCl_2$), 7.18 (2H, B part of AB q, J=8.5 Hz, ArH-2 and ArH-6), 7.36 (2H, A part of AB q, J=8.3 Hz, ArH-3′ and ArH-5′), 7.75 (2H, B part of AB q, J=8.3 Hz, ArH-2′ and ArH-6′). ^{13}C-NMR ($CDCl_3$) δ: 21.8 (q), 52.9 (q), 66.3 (d), 122.5 (d), 128.5 (d), 129.9 (d), 130.7 (d), 131.1 (s), 132.0 (s), 132.4 (s), 138.7 (d), 145.7 (s), 150.0 (s), 165.8 (s). MS *m/z*: 414 (M^+), 91 (base). *Anal.* Calcd for $C_{18}H_{16}Cl_2O_5S$: C, 52.06; H, 3.88. Found: C, 52.29; H, 3.87.

The second fraction contained 2-*t*-dichloromethyl-3-*r*-methoxycarbonyl-3-*t*-[4-(*p*-toluenesulfonyloxy)phenyl]-2,3,3a, 4,5,6-hexahydropyrrolo[1,2-*b*]isoxazole (**7**) (0.8 g, 10%) as colorless plates, mp 138—140 °C (chloroform–hexane). IR ν_{max}^{KBr} cm^{-1}: 1760, 1370, 1160. ^{1}H-NMR ($CDCl_3$) δ: 1.58—1.83 (2H, m, CCH_2C), 1.96—2.13 (2H, m, methylene), 2.44 (3H, s, $ArCH_3$), 3.35 (2H, m, H_2-6), 3.80 (3H, s, CO_2CH_3), 3.98 (1H, t, J=8.2 Hz, H-3a), 4.76 (1H, d, J=7.9 Hz, H-2), 4.96 (1H, d, J=7.9 Hz, $CHCHCl_2$), 6.99 (2H, A part of AB q, J=8.7 Hz, ArH-3 and ArH-5), 7.28 (2H, B part of AB q, J=8.7 Hz, ArH-2 and ArH-6), 7.42 (2H, A part of AB q, J=8.5 Hz, ArH-3′ and ArH-5′), 7.66 (2H, B part of AB q, J=8.5 Hz, ArH-2′ and ArH-6′). ^{13}C-NMR ($CDCl_3$) δ: 21.7 (q), 23.7 (t), 29.4 (t), 52.6 (q), 57.8 (t), 68.9 (s), 70.1 (d), 76.3 (d), 83.6 (d), 122.1 (d), 128.6 (d), 129.7 (d), 130.5 (d), 131.9 (s), 135.1 (s), 145.6 (s), 149.3 (s), 171.3 (s). MS *m/z*: 499 (M^+), 91 (base). *Anal.* Calcd for $C_{22}H_{23}Cl_2NO_6S$: C, 52.81; H, 4.63; N, 2.80. Found: C, 52.60; H, 4.55; N, 2.83.

The third fraction contained 3-*t*-dichloromethyl-2-*r*-methoxycarbonyl-2-*t*-[4-(*p*-toluenesulfonyloxy)phenyl]-2,3,3a,4,5,6-hexahydropyrrolo[1,2-*b*]isoxazole (**6**) (4.2 g, 52%) as colorless crystals, mp 126—127 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725, 1365, 1100. ^{1}H-NMR ($CDCl_3$) δ: 1.75—2.25 (4H, series of m, H_2-4 and H_2-5), 2.44 (3H, s, $ArCH_3$), 3.28 (2H, m, H_2-6), 3.75 (3H, s, OCH_3), 4.10 (2H, m, H-3 and H-3a), 5.39 (1H, d, J=3.6 Hz, $CHCl_2$), 6.99 (2H, A part of AB q, J=8.7 Hz, ArH-3 and ArH-5), 7.27 (2H, B part of AB q, J=8.7 Hz, ArH-2 and ArH-6), 7.46 (2H, A part of AB q, J=8.5 Hz, ArH-3′ and ArH-5′), 7.65 (2H, B part of AB q, J=8.5 Hz, ArH-2′ and ArH-6′). ^{13}C-NMR ($CDCl_3$) δ: 21.7 (q), 23.8 (t), 31.3 (t), 53.5 (q), 57.2 (t), 65.2 (d), 67.6 (d), 71.9 (d), 89.1 (s), 122.5 (d), 127.7 (d), 128.6 (d), 129.7 (d), 131.9 (s), 134.0 (s), 145.6 (s), 149.7 (s), 171.9 (s). MS *m/z*: 499 (M^+), 91 (base). *Anal.* Calcd for $C_{22}H_{23}Cl_2NO_6S$: C, 52.81; H, 4.63; N, 2.80. Found: C, 52.57; H, 4.60; N, 3.05.

1-Aza-4-*c*-chloromethyl-3-*r*-hydroxy-3-*t*-[4-(*p*-toluenesulfonyloxy)-phenyl]bicyclo[3.3.0]octan-2-one (11)——Zinc dust (4 g) was added in small portions to a stirred solution of **6** (1.0 g, 2.0 mmol) in 50% aqueous acetic acid (50 ml), and the mixture was stirred at 50—60 °C for 48 h. The mixture was basified with 30% NaOH and extracted with chloroform. The organic layer was washed with water, dried (Na_2SO_4), and evaporated. The residue was recrystallized from benzene to give **11** (0.75 g, 86%) as colorless needles, mp 177—178 °C. IR $\nu_{max}^{CDCl_3}$ cm^{-1}: 3540, 3275 (br), 1670, 1370, 1150. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (1H, m, HCH), 2.1—2.35 (4H, m, CH_2, HCH, and H-4), 2.46 (3H, s, $ArCH_3$), 3.17 (1H, m, HCHCl), 3.4—3.6 (2H, m, HCHCl and H-7), 3.75 (1H, t, J=12.1 Hz, H-7), 3.75—3.9 (1H, m, H-4a), 4.55 (1H, s, OH), 6.92 (2H, A part of AB q, J=8.5 Hz, ArH-3 and ArH-5), 7.17 (2H, B part of AB q, J=8.5 Hz, ArH-2 and ArH-6), 7.34 (2H, A part of AB q, J=8.3 Hz, ArH-3′ and ArH-5′), 7.73 (2H, B part of AB q, J=8.3 H, ArH-2′ and ArH-6′). MS *m/z*: 435 (M^+), 91 (base). *Anal.* Calcd for $C_{21}H_{22}ClNO_5S$: C, 57.86; H, 5.09; N, 3.21. Found: C, 57.82; H, 5.03; N, 2.90.

1-Aza-3-*r*-hydroxy-4-*c*-methyl-3-*t*-[4-(*p*-toluenesulfonyloxy)phenyl]bicyclo[3.3.0]octan-2-one (12). Procedure A. From 11——Zinc dust (2 g) was added in small portions to a stirred solution of **11** (200 mg, 0.46 mmol) in 90% aqueous acetic acid (15 ml), and the mixture was stirred at 130 °C for 5 h. Work-up similar to that described above for **6** followed by recrystallization from benzene gave **12** (170 mg, 92%) as colorless needles, mp 190—192 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540, 3300 (br), 1675, 1365, 1145. ^{1}H-NMR ($CHCl_3$) δ: 0.98 (3H, d, J=8.3 Hz, 4-CH_3), 1.34 (1H, m, $HCHCH_2$), 1.83 (1H, quint., J=8.3 Hz, $CHCH_3$), 2.14 (3H, m, $HCHCH_2$), 2.46 (3H, s, $ArCH_3$), 3.20 (1H, m, H-7),

3.46 (1H, s, OH), 3.56 (1H, m, H-7), 3.67 (1H, m, H-4a), 6.95 (2H, A part of AB q, J=8.5 Hz, ArH-3 and ArH-5), 7.25—7.37 (4H, ArH), 7.71 (2H, B part of AB q, J=8.3 Hz, ArH-2′ and ArH-6′). ^{13}C-NMR ($CDCl_3$) δ: 8.7 (q), 21.7 (q), 27.0 (t), 30.1 (t), 41.0 (t), 51.8 (d), 65.0 (d), 85.4 (s), 121.7 (d), 127.4 (d), 128.5 (d), 129.8 (d), 132.5 (s), 140.2 (s), 145.3 (s), 148.8 (s), 173.0 (s). MS m/z: 401 (M^+), 70 (base). *Anal.* Calcd for $C_{21}H_{23}NO_5S$: C, 62.83; H, 5.77; N, 3.49. Found: C, 62.54; H, 5.71; N, 3.25.

Procedure B. From 6——Zinc dust (6 g) was added in small portions to a stirred solution of **6** (1.0 g, 2.0 mmol) in 90% aqueous acetic acid (50 ml), and the mixture was stirred at 130—140 °C for 24 h. Usual work-up followed by recrystallization from benzene gave **12** (0.7 g, 87%), which was identical with the sample prepared above in procedure A.

Methyl 2-Phenyl-3-butenoate (15)——A solution of diazomethane [generated from *N*-nitrosomethylurea (8.0 g, 0.39 mol) and 40% KOH (60 ml)] in ether (80 ml) was added a solution of **14**[8] (1.6 g, 9.9 mmol) in ether (20 ml). The mixture was allowed to stand at room temperature for 72 h, then washed with saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). Evaporation of the solvent gave an oily residue, which was purified by column chromatography on silica gel with benzene–hexane (10 : 90) to afford **15** (1.53 g, 88%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1630, 990, 920. ^{1}H-NMR ($CDCl_3$) δ: 3.70 (3H, s, CO_2CH_3), 4.32 (1H, d, J=8.2 Hz, ArC<u>H</u>), 5.14 (1H, d, J=17.1 Hz, $\underline{H}C{=}C(H)\underline{H}$), 5.21 (1H, d, J=9.9 Hz, $\underline{H}C{=}C(H)\underline{H}$), 6.22 (1H, ddd, J=17.1, 9.9, 8.2 Hz, C<u>H</u>=CH_2), 7.30 (5H, m, phenyl). MS m/z: 176 (M^+), 117 (100). High-resolution MS m/z: Calcd for $C_{11}H_{12}O_2$ (M^+) 176.0837. Found 176.0853.

Cycloaddition of Butenoate (15) with 1-Pyrroline 1-Oxide (5)——A mixture of **15** (1.70 g, 9.65 mmol) and **5** (0.83 g, 9.75 mmol) in toluene (15 ml) was heated under reflux for 6 h. The solvent was evaporated off under reduced pressure and the residue was chromatographed on a silica gel column. Elution with diisopropyl ether–benzene (10 : 90) furnished an oil, which gave two spots on TLC. Separation of this oily mixture by preparative TLC [silica gel, diisopropyl ether–benzene (50: 50)] yielded 3-methoxycarbonyl-2-methyl-3-phenyl-2,3,3a,4,5,6-hexahydropyrrolo[1,2-*b*]isoxazole (**18**) (800 mg, 32%) as the less polar component and its regioisomer (**17a** or **17b**) (400 mg, 16%) as the more polar component. The former product (**18**) crystallized on standing, mp 81—82 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, d, J=6.3 Hz, 2-CH_3), 3.10 (1H, m, H-6), 3.53 (1H, m, H-6), 3.75 (3H, s, CO_2CH_3), 4.13 (1H, t, J=8.3 Hz, H-3a), 4.50 (1H, q, J=6.3 Hz, H-2), 7.24—7.39 (5H, phenyl). ^{13}C-NMR ($CDCl_3$) δ: 13.6 (q), 24.2 (t), 30.5 (t), 51.9 (q), 58.2 (t), 69.0 (s), 72.3 (d), 74.2 (d), 127.3 (d), 128.1 (d), 128.2 (d), 137.8 (s), 172.6 (s). MS m/z: 261 (M^+), 86 (base). *Anal.* Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.08; H, 7.35; N, 5.17.

Compound **17a** (or **17b**), obtained as a colorless oil, exhibited the following spectral properties: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725. ^{1}H-NMR 0.83 (3H, d, J=7.4 Hz, 3-CH_3), 3.09 (1H, m, H-3), 3.30 (2H, m, H-3a and H-6), 3.75 (3H, s, CO_2CH_3), 7.25—7.65 (5H, phenyl). ^{13}C-NMR ($CDCl_3$) δ: 15.1 (q), 22.7 (t), 27.8 (t), 49.4 (d), 52.8 (q), 57.0 (t), 71.7 (d), 91.0 (s), 126.0 (d), 127.7 (d), 128.1 (d), 137.5 (s), 172.5 (s). MS m/z: 261 (M^+), 86 (base). High-resolution MS m/z: Calcd for $C_{15}H_{19}NO_3$ (M^+) 261.1364. Found 261.1368.

Further elution with the same solvent system in the above column chromatography gave a mixture of oily products. Separation of this mixture by preparative TLC [silica gel, diisopropyl ether–chloroform (50 : 50)] afforded colorless oily **17b** (or **17a**) (370 mg, 15%) as the less polar component. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, d, J=7.4 Hz, 3-CH_3), 2.27 (1H, m, H-3), 3.58 (1H, m, H-3a), 3.74 (3H, s, CO_2CH_3), 7.24—7.50 (5H, phenyl). ^{13}C-NMR ($CDCl_3$) δ: 13.8 (q), 23.1 (t), 30.1 (t), 52.4 (q), 55.1 (d), 57.6 (t), 72.5 (d), 88.2 (s), 125.1 (d), 128.0 (d), 128.3 (d), 138.5 (s), 172.0 (s). MS m/z: 261 (M^+), 86 (base). High-resolution MS m/z: Calcd for $C_{15}H_{19}NO_3$ (M^+) 261.1364. Found 261.1390.

The more polar colorless oily product was identified as methyl 2,3,3aα,4,5,6-hexahydropyrrolo[1,2-*b*]isoxazol-2α-yl phenylacetate (**16a** and **16b**) (430 mg, 17%), and was considered to be a 6 : 5 mixture of diastereomers on the basis of ^{1}H-NMR and ^{13}C-NMR spectral analysis. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725. ^{1}H-NMR ($CDCl_3$) δ: 3.28 and 3.09 [total 1H (6 : 5 ratio), each m, H-3a], 3.73 and 3.79 [total 1H (6 : 5 ratio), each d, J=9.7 Hz, ArC<u>H</u>], 4.76 and 4.63 [total 1H (6 : 5 ratio), each dt, J=9.7, 7.6 Hz, H-2), 7.27—7.40 (5H, phenyl). In the ^{13}C-NMR spectrum of the product (the diastereomeric mixture of **16a** and **16b**), each carbon appeared as a pair of signals with the same multiplicity except in a few cases. The signal with weaker intensity in each pair is indicated in parentheses as follows: ^{13}C-NMR ($CDCl_3$) δ: 24.2 (t), 31.5 (t), 40.1 (41.4) (t), 52.1 (q), 55.9 (55.5) (d), 57.1 (56.9) (t), 65.2 (65.1) (d), 77.9 (78.3) (d), 127.8 (127.6) (d), 128.4 (d), 128.8 (128.6) (d), 135.7 (136.5) (s), 172.9 (172.4) (s). MS m/z: 261 (M^+), 91 (base). High-resolution MS m/z: Calcd for $C_{15}H_{19}NO_3$ (M^+) 261.1364. Found 261.1392.

Isomerization of Butenoate 15——A mixture of **15** (188 mg, 1.00 mmol) and triethylamine (101 mg, 1.00 mmol) in toluene (5 ml) was heated under reflux for 4 h and the solvent was removed by evaporation *in vacuo*. The residue was analyzed by ^{1}H-NMR spectroscopy and GLC to generate **15** (45%), methyl (*E*)-2-phenyl-2-butenoate (**19a**) (37%), and methyl (*Z*)-2-phenyl-2-butenoate (**19b**) (18%).

The data for **19a** were as follows: ^{1}H-NMR ($CDCl_3$) δ: 2.05 (3H, d, J=8.3 Hz, =CHC<u>H</u>$_3$), 3.80 (3H, s, CO_2CH_3), 6.27 (1H, q, J=8.3 Hz, =C<u>H</u>CH_3).

The data for **19b** were as follows: ^{1}H-NMR ($CDCl_3$) δ: 1.74 (3H, d, J=8.3 Hz, $=CHC\underline{H}_3$), 3.73 (3H, s, CO_2CH_3), 7.17 (1H, unresolved, $=C\underline{H}CH_3$).

GLC t_R values (90 °C) for these products (**15**, **19a**, and **19b**) were 2.1, 3.0 and 3.2 min, respectively.

1-Aza-4β-hydroxy-3α-phenyl-5aα*H*-bicyclo[4.3.0]nonan-2-one (20)——Zinc dust (2 g) was added to a solution of **16** (100 mg, 0.38 mmol) in 90% aqueous acetic acid (10 ml) and the mixture was heated at 120 °C with stirring. After 8 h the mixture was basified with aqueous NaOH and extracted with chloroform. The organic layer was washed with saturated aqueous NaCl and dried (Na_2SO_4). Evaportion of the solvent and recrystallization of the product from benzene gave **20** (40 mg, 45%) as colorless needles, mp 171—172 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350, 1625. ^{1}H-NMR ($CDCl_3$) δ: 1.45—2.30 (6H, series of m, H-5, H_2-6, H_2-7, and OH), 2.41 (1H, br d, J=14.5 Hz, H-5), 3.36 (1H, d, J=9.8 Hz, H-3), 3.40—3.68 (3H, m, H-5a and H_2-8), 4.01 (1H, m, H-4), 7.20—7.38 (5H, m, phenyl). ^{13}C-NMR ($CDCl_3$) δ: 22.5 (t, C-7), 33.2 (t, C-6), 37.4 (t, C-5), 45.2 (t, C-8), 55.8 (d, C-3 or C-5a), 58.3 (d, C-5a or C-3), 72.3 (d, C-4), 127.1 (d, C-4′), 128.6 (d, C-2′ and C-6′), 129.1 (d, C-3′ and C-5′), 139.0 (s, C-1′), 168.7 (s, C-2). MS m/z: 231 (M^+), 114 (base). *Anal.* Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.73; H, 7.36; N, 6.00.

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