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Birch Reduction of (−)-Ephedrine. Formation of a New, Versatile Intermediate for Organic Synthesis

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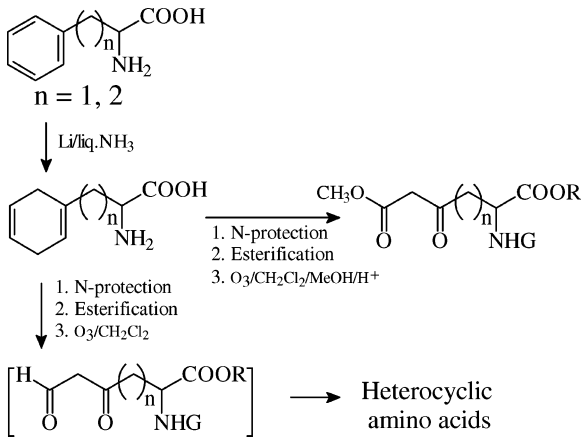
Abstract: The reduction of (−)-ephedrine by lithium in liquid ammonia resulted in the formation of *S*-1-(1,4-cyclohexadien-1-yl)-*N*-methyl-2-propanamine. In addition to the reduction of the aromatic ring, the hydroxy group was reduced as well. The resulting 1,4-cyclohexadienyl group is a potentially versatile intermediate for further synthetic transformations. The ozonolysis of this group was investigated, producing derivatives of *β*-keto-*δ*-methylamino esters and *β*-keto aldehydes which could be subsequently converted to heterocycles. The restriction to rotation of the C−N bond in *N*-benzoyl-1-(1,4-cyclohexadien-1-yl)-*N*-methyl-2-propanamine is described.

In the late 1990s, we investigated the transformation of aromatic amino acids such as phenylalanine and phenylglycine to functionalized amino acids by the combination of Birch reduction of the benzene ring followed by ozonolysis. We reported the synthesis of various new heterocyclic α-amino acids (Scheme 1) by using this methodology.[1−5] Recently, we have also found that ozonolysis of 1,4-cyclohexadiene derivatives in the presence of methanol and acid can lead to *β*-keto esters (Scheme 1).[6]

In the present work, (−)-ephedrine (**1**) was treated with lithium in liquid ammonia at −70 °C. *tert*-Butyl alcohol was used as a proton donor. Both the phenyl and the hydroxyl were reduced in these conditions to yield 1-(1,4-cyclohexadien-1-yl)-*N*-methyl-2-propanamine (**2**, Scheme 2). The ozonolysis of the resulting 1,4-cyclohexadienyl group was investigated, showing the possibility of derivatization. It was assumed that the chiral center in **2** and **3**, which is two carbons away from the functionalized group is not affected by this sequence of reactions.

In previous work, it was found[1−4] that for the purpose of treatment with ozone it was necessary to protect the amino group. The *N*-benzoyl-*N*-methyl-1-(1,4-cyclohexadien-1-yl)propanamine (**4**) was prepared and subjected to acid-catalyzed ozonolysis in the presence of methanol[6] resulting in methyl *N*-benzoyl-5-methylamino-3-oxohexanoate (**3**). Both the amide **4** and the ester **3** gave complex proton NMR spectra. The spectra had broad peaks of two conformers in each of these products. This phenomenon indicated that at room temperature there is some restriction to the rotation of the amidic C−N bond resulting in a slow equilibrium compared to the NMR time scale. Two conformers in about equal amounts were observed. By cooling to a lower temperature the signals sharpened. By heating to 430 K in DMSO-d_6 coalescence to one conformer occurred. This trend is known in substituted amides and was suggested many years ago by Pauling as part of the explanation of the secondary structure of proteins. There is a large difference between the chemical shift of the proton adjacent to the amide group in the two conformers of about 1.0 ppm in **4** and 0.9 ppm in **3**. The large difference is probably due to the "through space" deshielding effect of the carbonyl oxygen. The rotational barrier could be estimated from the coalescence temperature.[7] The calculated free energy of activation

SCHEME 1



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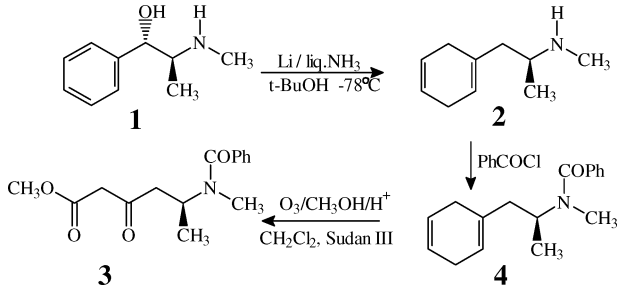

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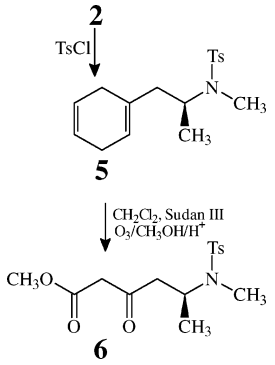

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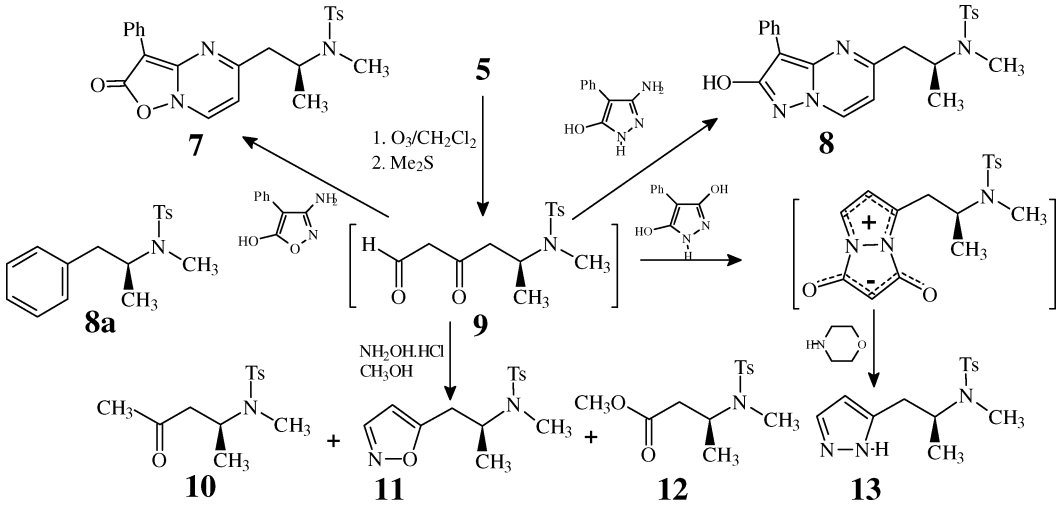
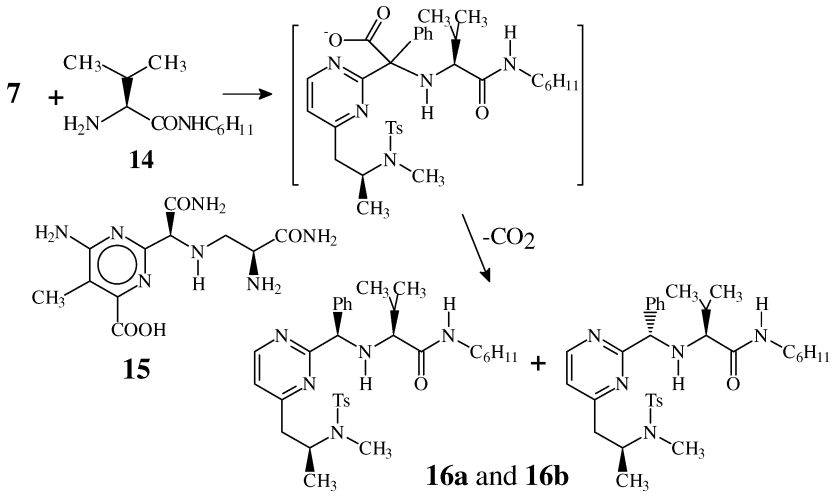
SCHEME 4



SCHEME 5



($\Delta G^{\ddagger}$'s) in DMSO-d_6 were 16.0 ± 1 and 13.7 ± 1 kcal mol^{-1} for **3** and **4**, respectively. One could observe about 10% of the enolate form of **3** in the NMR spectrum as well.

The *N*-tosyl derivative of **2** was also prepared and subjected to the same process, yielding the tosyl ester (**6**, Scheme 3). As expected, there was no restricted bond rotation in both **5** and **6** at room temperature.

As described previously,[1−4] it was impossible to isolate keto aldehydes such as **9** (Scheme 4). Upon treatment with ozone in methylene chloride at −78 °C, followed by treatment with dimethyl sulfide as a reducing agent, a major fragmentation occurred. In addition to formic acid, one product of partial fragmentation, e.g., *N*-methyl-4-oxo-*N*-tosyl-2-hexaneamine (**10**), was isolated. By reacting the ozonolysis reaction mixture directly with dinucleophiles, fair yields of heterocyclic derivatives (**7**, **8**, **11**, and **13**) were obtained (Scheme 4). However, in all experiments certain amounts of the chain contraction and rearomatization products (**10** and **8a**, respectively) were observed. The reaction with hydroxylamine in methanol to produce the isoxazole derivative (**11**) was accompanied by the formation of the amino ester **12** as well.

The rather unstable isoxazolopyrimidine derivative (**7**) was transformed by a nucleophilic ring opening[8] with *N*-cyclohexylvalinamide (**14**, Scheme 5) to **16**. The latter has a somewhat related structure to pyrimidoblamic acid (**15**). Pyrimidoblamic acid (**15**) is an important constituent of bleomycins, which are anticancer drugs.[9−11] The amino amide derivative which is obtained has three chiral centers, of which one was formed in this ring opening process. Thus, two stereoisomers (**16a** and **16b**) were obtained in a 1:2 ratio. The two diasteromers could be separated by column chromatography.

Experimental Section

Birch Reduction of (−)-Ephedrine. (−) Ephedrine (6 g, 0.036 mol) was placed in a 1 L flask on a dry ice−acetone bath with a dry ice condenser. Liquid ammonia (300 mL) was

(7) $\Delta G^{\ddagger}$ Values were calculated with the equation: $\Delta G^{\ddagger} = 4.58T_c[9.972 + \log(T_c/\Delta\nu)] \times 10^{-3}$ kcal mol^{-1} where T_c is the coalescence temperature and $\Delta\nu$ is the separation in Hz between the signals of the two conformers. See: Paek, K.; Ihm, H.; Yun, S.; Lee, H. C.; No, K. T. *J. Org. Chem*. **2001**, *66*, 5736.

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introduced, and then *tert*-butyl alcohol (100 mL) was added slowly during 1 h. Small pieces of lithium ribbon (3 g, 0.4 mol) were added during 6 h with stirring, retaining the blue color of the solution. The reaction mixture was stirred and allowed to warm to room temperature in the hood overnight, while most of the ammonia evaporated. Solvents were removed by vacuum, and the white residue was dissolved in water (150 mL). The resulting 1-(1,4-cyclohexadien-1-yl)-*N*-methyl-2-propanamine (**2**) was extracted by ethyl acetate (oil, 4 g, 73%). ^{1}H NMR (300 NHz, $CDCl_3$) δ: 5.67 (br s, 2H), 5.46 (br s, 1H), 2.68−2.54 (m, 5H), 2.36 (s, 3H), 2.01 (part A of double AB system, J = 13.3, 8.0 Hz, 1H), (part B of double AB system, J = 13.3, 6.0 Hz, 1H), 1.03 (d, J = 6.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: (132.1, 123.9, 123.9, 121.1, 51.8, 45.6, 33.9, 28.7, 26.5, 19.7).

For elemental analysis, a small portion was transformed into the HCl salt: The oil (0.05 g) was dissolved in dichloromethane (1 mL). Ethanolic HCl (4 N, 0.5 mL) and excess ether were added. The salt precipitated and was collected by filtration (0.05 g, mp 185 °C). ^{1}H NMR ($CDCl_3$) δ: 5.69 (br s, 2H), 5.60 (br s, 1H), 3.21 (m, 1H), 2.72−2.55 (m, 4H + s. 3H), 2.30 (d, J = 13.2 Hz, 1H), 2.26 (d, J = 13.2 Hz, 1H), 1.39 (d, J = 6.6 Hz, 3H). Anal. Calcd for $C_{10}H_{18}NCl$: C, 64.00; H, 9.67; N, 7.46. Found: C, 64.12; H, 9.59; N, 7.33

***N*-Benzoyl-1-(1,4-cyclohexadien-1-yl)-*N*-methyl-2-propanamine (4).** 1-(1,4-Cyclohexadien-1-yl)-*N*-methylpropanamine (**2**) (2 g, 13.2 mmol) was suspended in water (30 mL) and cooled on an ice−water bath. Benzoyl chloride (2 g, 14 mmol) and 2 N NaOH were added simultaneously during 2 h. The pH was kept at values 8−9. The reaction mixture was stirred on the ice−water bath for an additional 1 h and then stirred for 1 h at room temperature, keeping the pH between 8 and 9. The mixture was extracted with ethyl acetate. The organic layer was washed with dilute NaOH and then with 0.1 N HCl. The organic layer was dried on sodium sulfate and the solvent evaporated in a vacuum. The oily residue was purified on a silica gel column and eluted with a petroleum ether−ethyl acetate gradient (oil, 1.8 g, 53%). At temperatures below 150 °C, a coalescence of two conformers was observed in the NMR. ^{1}H NMR (DMSO-d_6, T = 430 K, 400 MHz) δ: 7.41−7.07 (m, 5H), 5.68 (br s, 2H), 5.44 (br s, 1H), 4.42−4.33 (m, 1H), 2.80 (s, 3H), 2.72−2.45 (m, 4H), 2.33−2.06 (m, 2H), 1.18 (d, J = 6.0 Hz, 3H). Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.73; H, 8.08; N, 5.49

Methyl *N*-Benzoyl-5-methylamino-3-oxohexanoate (3). *N*-Benzoyl-1-(1,4-cyclohexadien-1-yl)-*N*-methylpropanamine (**4**, 1 g, 4 mmol) was dissolved in dichloromethane (20 mL). *p*-Toluenesulfonic acid (0.2 g, 1.1 mmol), 5 mL of methanol, and a drop of a methanolic solution of Sudan III indicator were added. The dilution of the indicator solution was adjusted so that the reaction mixture had a very slight pink color. The solution was cooled on an acetone−dry ice bath (−78 °C), and a mixture of ozone and oxygen was passed carefully until the light pink color faded. After the mixture was allowed to stand for 72 h at room temperature, the solvent was evaporated to a small volume and loaded on a silica gel column. Upon elution with petroleum ether−ethyl acetate gradient the keto ester methyl *N*-benzoyl-5-methylamino-3-oxohexanoate **(3)** was obtained, 0.6 g (oil, 55%). At temperatures below 150 °C, a coalescence of two conformers was observed in the NMR. ^{1}H NMR (DMSO, 400 MHz, T = 430 K) δ: 7.46−7.32 (m, 5H), 4.54 (m, 1H), 3.68 (s, 3H,), 3.25 (s, 2H), 2.79 (s, 3H), 2.83 (part A of partly hidden double AB system, J = 16.0, 6.9 Hz, 1H), 1.21 (d, J = 6.7 Hz, 3H), 2.68 (part B of partly hidden doubleAB system, J = 16.0, 6.9 Hz, 1H), 1.21 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, T = 298 K) δ: (172.1, 171.5, 170.6, 129.3, 128.3, 126.7, 126.3, 51.8, 51,0, 46.8, 38.8, 38.3, 31.9, 26.3, 18.8, 17.5). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.70; H, 7.15; N, 5.08

1-(1,4-Cyclohexadien-1-yl)-*N*-methyl-*N*-tosyl-2-propanamine (5). 1-(1,4-Cyclohexadien-1-yl)-*N*-methyl-2-propanamine (**2**) (3.5 g, 23 mmol) was suspended in water (50 mL) and cooled on an ice−water bath. Tosyl chloride (4.5 g, 23.6 mmol) and 2 N NaOH were added simultaneously during 2 h. The pH was kept at values of 9−10. The reaction mixture was stirred on the ice−water bath for an additional 1 h and then stirred for 1 h at room temperature, keeping the pH between 9 and 10. The mixture was extracted with ethyl acetate. The organic layer was washed with dilute NaOH and then with 0.1 N HCl. The organic layer was dried on sodium sulfate and the solvent evaporated in a vacuum. The oily residue was purified on a silica gel column, eluted with petroleum ether−ethyl acetate gradient (oil, 4.5 g, 64%). ^{1}H NMR (300 NHz, $CDCl_3$) δ: 7.67 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 5.66 (br s, 2H), 5.38 (br s, 1H), 4.26−4.13 (m, 1H), 2.66 (s, 3H), 2.65−2.55 (m, 4H), 2.38 (s, 3H), 2.04−1.91 (m, 2H), 0.95 (d, J = 6.9 Hz, 3H). ^{13}C NMR (300 NHz, $CDCl_3$) δ: (142.8, 137.0, 131.3, 129.4, 127.0, 124.0, 123.7, 121.5, 50.3, 42.6, 29.4, 27.3, 26.7, 21.4, 17.0). Anal. Calcd for $C_{17}H_{23}NO_2S$: C, 66.85; H, 7.59; N, 4.59. Found: C, 66.84; H, 7.36; N, 4.57.

Methyl 5-Methylamino-3-oxo-*N*-tosylhexanoate (6). 1-(1,4-Cyclohexadien-1-yl)-*N*-methyl-*N*-tosyl-2-propanamine (**5**, 1 g, 3.2 mmol) was dissolved in dichloromethane (20 mL). *p*-Toluenesulfonic acid (0.2 g, 1.1 mmol), 5 mL of methanol, and a drop of a methanolic solution of Sudan III indicator were added. The dilution of the indicator solution was adjusted so that the reaction mixture had a very slight pink color. The solution was cooled on an acetone−dry ice bath (−78 °C), and a mixture of ozone and oxygen was passed carefully until the light pink color faded. After the mixture was allowed to stand for 72 h at room temperature, the solvent was evaporated to a small volume and loaded on a silica gel column. Upon elution with petroleum ether−ethyl acetate gradient the keto ester methyl 5-methylamino-3-oxo-*N*-tosylhexanoate **(6)** was obtained, 0.42 g (oil, 40%). The NMR revealed a 7:1 mixture of tautomers. ^{1}H NMR of major tautomer ($CDCl_3$, 300 MHz) δ: 7.66 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 4.51 (m, 1H), 3.70 (s, 3H), 3.52 (part A of AB system, J = 16.0 Hz, 1H), 3.40 (part B of AB system, J = 16.0 Hz, 1H) 1H), 2.70 (s, 3H), 2.60 (br s, 5H), 2.44 (part A of partly hidden double AB system, J = 16.4, 6.1 Hz, 1H), 1.21 (d, J = 6.7 Hz, 3H), 2.68 (part B of partly hidden double AB system, J = 16.4, 6.1 Hz, 1H), 2.40 (s, 3H), 0.92 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: (199.9, 167.3, 143.3, 129.6, 127.1, 90.6, 52.5, 49.0, 48.7, 47.8, 28.4, 21.3, 17.0). Anal. Calcd for $C_{15}H_{21}NO_5S$: C, 55.03; H, 6.47; N, 4.28; S, 9.79. Found: C, 55.17; H, 6.40; N, 4.46; S, 9.59

Reaction of 1-(1,4-Cyclohexadien-1-yl)-*N*-methyl-*N*-tosyl-2-propanamine (5) with Ozone. Dichloromethane (20 mL), buffered with 0.1 of $NaHCO_3$, was saturated with ozone at −70 °C. 1-(1,4-Cyclohexadien-1-yl)-*N*-methyl-*N*-tosyl-2-propanamine (**5**, 1.0 g, 3.2 mmol) was added, and more ozone was introduced until the blue color persisted. After the reaction mixture was washed with nitrogen, dimethyl sulfide (10 mL) was added and the solution left at room temperature overnight. After filtration, the solvent was removed and the residue suspended in ethyl acetate (1 mL), and the resulting products were isolated by silica gel column chromatography. Two products were identified. None was the expected aldehyde **9**. One fraction was a very minor amount of rearomatized product *N*-methyl-1-phenyl-*N*-tosyl-2-propanamine **8a** (0.05 g, oil). ^{1}HNMR ($CDCl_3$) δ: 7.57 (d, J = 8.1 Hz, 2H), 7.28−7.20 (m, 5H), 7.12 (d, J = 8.1 Hz, 2H), 4.32−4.27 (m, 1H), 2.74 (s, 3H), 2.59 (m, 2H), 2.39 (s, 3H), 0.96 (d, J = 6.72, 3H). Anal. Calcd for $C_{17}H_{21}NO_2S$: C, 67.29; H, 6.98; N, 4.62. Found: C, 67.09; H, 7.10; N, 4.58.

The second identified product was the cleavage product *N*-methyl-4-oxo-*N*-tosyl-2-pentanamine (**10**, oil, 0.33 g 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.65 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 4.52−4.45 (m, 1H), 2.69 (s, 3H), 2.47 (d, J = 7.0 Hz, 2H), 2.40 (s, 3H), 2.02 (s, 3H), 0.91 (d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ: (205.8, 143.3, 136.5, 129.7, 127.1, 49.3, 48.8, 30.0, 28.4, 21.5, 17.3). Anal. Calcd for $C_{13}H_{19}NO_3S$: C, 57.97; H, 7.11; N, 5.20. Found: C, 57.74; H, 7.10; N, 5.24.

Reaction of 1-(1,4-Cyclohexadien-1-yl)-*N*-methyl-*N*-tosyl-2-propanamine (5) with Ozone Followed by Treatment with Hydroxylamine. Dichloromethane (15 mL), buffered with 0.1 of $NaHCO_3$, was saturated with ozone at −78°C. 1-(1,4-Cyclohexadien-1-yl)-*N*-methyl-*N*-tosyl-2-propanamine (**5,** 0.7 g, 3.3 mmol) was added, and more ozone was introduced until the blue color persisted. After the reaction mixture was washed with

nitrogen, dimethyl sulfide (10 mL) was added and the solution left at room temperature overnight. After filtration, the solvent was removed, the residue was dissolved again in methanol (20 mL), and hydroxylamine hydrochloride (0.32 g, 50 mmol) was added. The solution was refluxed for 5 h, ice−water (50 mL) was added, and the solution was neutralized to pH = 7 by $NaHCO_3$ and extracted with ethyl acetate. The organic layer was dried on Na_2SO_4, evaporated, and subjected to column chromatography. Upon elution with petroleum ether−ethyl acetate gradient, in addition to the desired isoxazole derivative (**11**), two additional products were identified (**10** and **12**). Ester **12**, oil (0.1 g, 15%). ^{1}H NMR ($CDCl_3$) δ: 7.70 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 4.49 (m, 1H), 3.64 (s, 3H), 2.72 (s, 3H), 2.44 (s, 3H), 2.41−2.31 (m, 2H), 0.86 (d, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: (171.0, 145.1, 136.7, 129.7, 127.1, 51.8, 50.1, 38.7, 28.1, 21.5, 17.4). Anal. Calcd for $C_{13}H_{19}NO_3S$: C, 54.72; H, 6.71; N, 4.91. Found: C, 54.32; H, 6.99; N, 4.90. Main product, 1-(isoxazol-5-yl)-*N*-methyl-*N*-tosyl-2-propanamine (**11**), oil (0.2 g, 31%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.12 (d, J = 1.7 Hz, 1H), 7.61 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H), 6.11 (d, J = 1.7 Hz), 4.45−4.38 (m, 1H), 2.83 (dd, J_1 = 7.4 Hz, J_2 = 4.7 Hz, 2H), 2.69 (s, 3H), 2.39 (s, 3H**),** 0.96 (d, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: (168.8, 150.3, 143.3, 136.4, 129.7, 127.0, 101.6, 51.5, 31.6, 27.7, 21.4, 17.0). Anal. Calcd for $C_{14}H_{18}N_2O_3S$: C, 57.12; H, 6.16; N, 9.52. Found: C, 57.13; H, 6.28; N, 9.28.

***N*-Methyl-1-(2-oxo-3-phenylisoxazolo[2,3-*a*]pyrimidin-5-yl)-*N*-tosyl-2-propanamine (7).** Dichloromethane (20 mL), buffered with 0.1 of $NaHCO_3$, was saturated with ozone at −78 °C. 1-(1,4-Cyclohexadien-1-yl)-*N*-methyl-*N*-tosyl-2-propanamine (**5**, 0.5 g, 1.6 mmol) was added, and more ozone was introduced until the blue color persisted. After the reaction mixture was washed with nitrogen, dimethyl sulfide (5 mL) was added and the solution left at room temperature overnight. After filtration, the solvent was removed and the residue dissolved again in 1 N ethanolic HCl. 3-Amino-5-hydroxy-3-phenylisoxazole[7] was added and the solution refluxed for 20 min, under argon and protected from light. Ice−water was added, the oil that separated was extracted with ethyl acetate, the solvent was evaporated and suspended in ethyl acetate (1 mL), and the product was isolated by silica gel column chromatography. The product **7** was eluted from the column by petroleum ether−ethyl acetate gradient, 0.3 g (orange-yellow semisolid). ^{1}H NMR (300 NHz, $CDCl_3$) δ: 8.20 (d, J = 7.8 Hz, 2H), 7.94 (d, J = 7.1 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.41 (t, J = 7.8 Hz, 2H), 7.21 (t, J = 7.8 Hz, 1H), 7.10 (d, J = 8.0 Hz, 2H) 6.41 (d, J = 7.1 Hz, 1H), 4.58−4.51 (m, 1H), 2.85 (s, 3H), 2.81−2.65 (partially hidden double AB system, 2H), 2.35 (s, 3H), 1.10 [d, J = 6.6 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: (169.1, 165.7, 152.6, 143.4, 136.8, 133.0, 130.1, 129.4, 128.2, 126.6, 125.5, 125.0, 105.2, 81.1, 52.7, 43.3, 27.8, 18.1, 15.4). ESI-HRMS (MH^+ *m*/*z*): 460.1287 (calcd for $C_{23}H_{23}N_3O_4S$ + Na 460.1306).

Ring-Opening Process of *S*-*N*-Methyl-3-(5-methyl-2-oxo-3-phenylisoxazolo[2,3-*a*]pyrimidin-7-yl)-*N*-tosyl-2-propanamine (7) by L-*N*-Cyclohexylvalinamide To Produce 16. *S*-*N*-Methyl-3-(5-methyl-2-oxo-3-phenylisoxazolo[2,3-*a*]pyrimidin-7-yl)-*N*-tosyl-2-propanamine (**7**) (0.085 g, 0.19 mmol) was dissolved in dioxane (10 mL). L-*N*-Cyclohexylvalinamide (0.04 g, 0.2 mmol) was added, and the mixture was refluxed in the dark and under argon for 18 h. The reaction was monitored by TLC and NMR of aliquots. The solvent was removed by evaporation in a vacuum. The ratio of isomers was determined by NMR (2:1) and the residue loaded on silica gel column and eluted with ethyl acetate−petroleum ether gradient (40−100%). The isomer that came first out of the column was **16a**, oil (0.03 g, 26% yield). ^{1}H NMR ($CDCl_3$) δ: 8.50 (d, J = 5.1 Hz, 1H), 7.50 (d, J = 8.1 Hz, 2H), 7.39−7.23 (m, 5H), 7.14 (d, J = 8.1 Hz), 6.98 (d, J = 5.1 Hz, 1H), 4.85 (s, 1H), 4.49 (m, 1H), 3.81−3.71 (m, 1H), 2.91 (d, J = 4.1 Hz, 1H), 2.89−2.77 (m, 2H), 2.75 (s, 3H), 2.37 (s, 3H), 2.17−2.11 (m, 1H), 1.85−1.01 (m, 10H), 0.96 (m, 9H) ^{13}C NMR ($CDCl_3$) δ: (172.2, 170.2, 166.9, 157.1, 143.1, 142.2, 136.7, 129.6, 128.6, 127.4, 127.3, 126.9, 118.8, 67.29, 7.14, 52.6, 47.3, 42.5, 33.3, 32.8, 31.5, 31.2, 28.0, 25.5, 24.71, 21.4, 19.7, 17.7, 17.3). $[\alpha]^{25}_D$ = −53.8 ($CHCl_3$, c = 1). ESI-HRMS (MH^+ *m*/*z*): 614.3105 (calcd for $C_{33}H_{45}N_5O_3S$ + Na 614.3140). The second isomer was **16b** (0.016 g, 18% yield). ^{1}H NMR ($CDCl_3$) δ: 8.52 (d, J = 5.1 Hz, 1H), 7.53 (d, J = 8.1 Hz, 2H), 7.39−7.26 (m, 5H), 7.17 (d, J = 8.1 Hz), 7.00 (d, J = 5.1, 1H), 4.84 (s, 1H), 4.48 (m, 1H), 3.77 (m, 2H), 2.90−2.76 (m, 2H), 2.75 (s, 3H), 2.38 (s, 3H), 2.17 (m, 1H,), 1.82−0.85 (m, 19H). $[\alpha]^{25}_D$ = +20.6 ($CHCl_3$, c = 1). ESI-HRMS (MH^+ *m*/*z*): 614.3105 (calcd for $C_{33}H_{45}N_5O_3S$ + Na 614.3140).

1-(2-Hydroxy-3-phenylpyrazolo[1,5-*a*]pyrimidin-5-yl)-*N*-methyl-*N*-tosyl-2-propanamine (8). Dichloromethane (20 mL), buffered with 0.1 of $NaHCO_3$, was saturated with ozone at −70 °C. 1-(1,4-Cyclohexadien-1-yl)-*N*-methyl-*N*-tosyl-2-propanamine (**5**, 0.5 g, 1.6 mmol) was added, and more ozone was introduced until the blue color persisted. After the reaction mixture was washed with nitrogen, dimethyl sulfide (5 mL) was added and the solution left at room temperature overnight. After filtration, the solvent was removed and the residue dissolved again in 1 N ethanolic HCl. 3-Amino-5-hydroxy-3-phenylpyrazole[12] (0.57 g, 3,-25 mmol) was added and the solution refluxed for 20 min. Ice−water was added and the oil that separated extracted with ethyl acetate. The organic layer was separated, dried on $MgSO_4$, and evaporated to dryness. The product was obtained by silica gel column chromatography. The product **8** was eluted from the column by petroleum ether−ethyl acetate gradient, mp 211 °C (0.14 g, 20%). ^{1}H NMR (DMSO-d_6) δ: 8.30 (d, J = 7.5 Hz, 2H), 8.28 (d, J = 3.6 Hz, 1H), 7.40 (t, J = 7.5 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.16 (partially hidden t, 1H) 7.12 (d, J = 8.1 Hz, 2H), 6.78 (d, J = 3.6 Hz, 1H), 4.76 (m, 1H**),** 3.14 (m, 2H), 2.81 (s, 3H), 2.16 (s, 3H), 1.08 (d, J = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: (148.8, 146.1, 145.0, 143.3, 136.69, 133.2, 129.8, 128.5, 127.2, 126.5, 126.3, 125.0, 107.6, 91.7, 49.6, 35.0, 27.8, 21.3, 18.2). ESI-HRMS (MH^+ *m*/*z*): 459.1498 (calcd for $C_{23}H_{24}N_4O_3S$ + Na 459.1468).

1-(Pyrazol-3-yl)-*N*-methyl-*N*-tosyl-2-propanamine (13). Dichloromethane (20 mL), buffered with 0.1 of $NaHCO_3$, was saturated with ozone at −70 °C. 1-(1,4-Cyclohexadien-1-yl)-*N*-methyl-*N*-tosyl-2-propanamine (**5**, 0.7 g, 2.3 mmol) was added, and more ozone was introduced until the blue color persisted. After the reaction mixture was washed with nitrogen, dimethyl sulfide (5 mL) was added and the solution left at room temperature overnight. After filtration, the solvent was removed and the residue dissolved again in THF. 3,5-Dihydroxy-3-phenylpyrazole[13,14] (0.6 g, 3.4 mmol) was added and the solution left at room temperature for 48 h. Morpholine (0.5 g, 56 mmol) was added and left overnight at room temperature, while the red color of the paraionic intermediate faded. The solvent evaporated to dryness and the residue loaded on a silica gel column. The product (**13**) was eluted from the column by petroleum ether−ethyl acetate gradient. Oil (0.15 g, 22%). ^{1}H NMR ($CDCl_3$) δ: 7.55 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 2.0 Hz, 1H), 7.19 (d, J = 8.04, 2H), 6.05 (d, J = 2.0 Hz, 1H), 4.33 (m, 1H), 2.73 (dd, J_1 = 7.4 Hz, J_2 = 2.8 Hz), 2.65 (s, 3H), 2.32 (s, 3H), 0.88(d, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: (145.2, 143.0, 136.4, 133.2, 129.5, 126.9, 104.3, 52.8, 32.3, 27.7, 21.3, 16.6). ESI-HRMS (MH^+ *m*/*z*): 316.1092 (calcd for $C_{14}H_{19}N_3O_2S$ + Na 316.1096).

Supporting Information Available: General experimental data, NMR figures of dynamic equilibrium between conformers in **3** and **4**, copies of ^{1}HNMR and ^{13}CNMR of new products, and high-resolution MS of **7**, **8**, **13**, and **16a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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