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INTRAMOLECULAR HYDRIDE TRANSFER AND CYCLIZATION OF 5-OXO-N_a-TOSYL-14,21-DEHYDROSECODINE[1]

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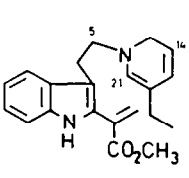
Abstract—5-Oxo-N_a-tosyl-14,21-dehydrosecodine (**8**) was prepared by bromination of **6** followed by double dehydrobromination with ethyl aluminum dichloride in HMPA. When a dilute solution of **8** was heated, **10** was formed via intramolecular hydride transfer and cyclization.

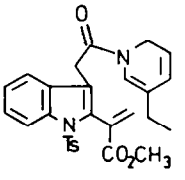
Over the years, a great deal of research has been devoted to the development of methods for the synthesis of *Aspidosperma* and *Iboga* alkaloids.[2] A number of reported approaches have involved the reaction of α-(indol-2-yl)acrylate systems with dihydro- or tetrahydropyridine derivatives.[3-9] These approaches are patterned after the proposed biosynthesis of the *Aspidosperma* and *Iboga* alkaloids from the putative intermediate 14,21-dehydrosecodine (**I**).[10,11] To date, the most successful strategies have involved either the inter-[3] or intramolecular[4] reactions of N-alkyl tetrahydropyridines with α-(indol-2-yl)acrylates to provide *Aspidosperma*-type systems, or the intermolecular cycloaddition of N-carboalkoxy dihydropyridines with α-(indol-2-yl)acrylates to provide precursors to *Iboga*-type systems.[5] In contrast, the intermolecular reactions of N-alkyl dihydropyridines with α-(indol-2-yl)acrylates have been less promising, due either to the formation of mixtures of skeletons[6] or substantial reduction of the acrylate systems by hydride transfer from dihydropyridines.[7] Attempts to generate N-alkyl dihydropyridine α-(indol-2-yl)acrylates and to investigate the intramolecular reactions of such species have also been fraught with difficulties.[8,9]

Based on the above results, it was our plan to prepare the N-acyl dihydropyridine α-(indol-2-yl)acrylate **8** and to study its mode of intramolecular reaction. It was our hope that **8** would undergo intramolecular reaction to provide the pentacyclic system **II** in a manner analogous to that reported by Sundberg[5] for his related intermolecular system. We now wish to report the regioselective synthesis of **8** and the results of studies concerning the reactions of this compound.

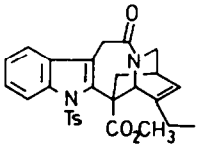
The preparation of **8** requires a method for the regioselective synthesis of an N-acyl-3-ethyl-1,6-dihydropyridine. Although Fowler has developed an excellent procedure for the preparation of N-carboalkoxy-1,2-dihydropyridines by the reaction of alkyl chloroformates, pyridine and sodium borohydride in methanol at −78°,[12] when this procedure is applied to 3-ethylpyridine, the major product is the undesired regioisomer, N-carboalkoxy-3-ethyl-1,2-dihydropyridine.[13] Furthermore, carboxylic acid chlorides can not be utilized in place of alkyl chloroformates in Fowler's procedure. Thus, it was decided to approach the requisite N-acyl-dihydropyridine by an oxidative process from an N-acyl-tetrahydropyridine, rather than by a reductive process from a pyridine.



I



8



II

We have developed a convenient strategy for the preparation of 2,3-disubstituted indoles based on the Claisen ortho ester rearrangement of indole-3-glycolic acid derivatives,[14] and we have recently extended this procedure to the preparation of α-(3-substituted-indol-2-yl)acrylates,[15] and applied it to the total synthesis of secodine.[16] Thus, the N-acyl-tetrahydropyridine **6** was easily prepared as outlined in Scheme 1.

The most attractive approach for the regioselective

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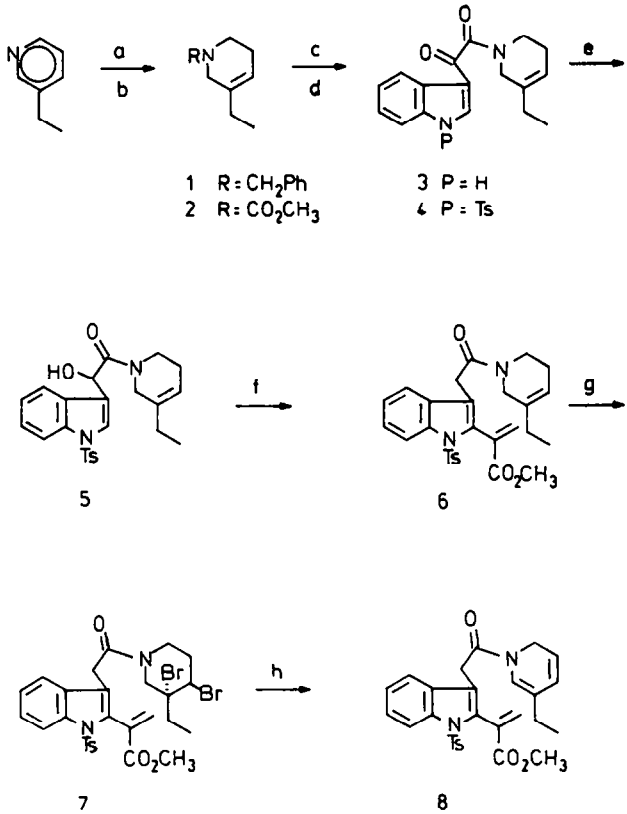
preparation of the N-acyl-dihydropyridine **8** appeared to be bromination/double dehydrobromination of **6**. Reaction of **6** with one equivalent of bromine in methylene chloride at $-78°$ gave the dibromide **7** in 93% yield with no evidence for competing reaction by the acrylate or indole moieties. A number of conventional procedures were investigated for the double dehydrobromination of **7** including quinoline at 150°;[17] 1,4-diazabicyclo[2.2.2]octane (DABCO) in DMF at 150°; 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF at 120° or CCl_4 at 77°;[18] or pyridine at reflux. In all instances, and depending on the length of the reaction time, either the dibromide **7** was recovered, or extensive decomposition accompanied by the formation of varying amounts of a by-product, later identified as **10**, occurred. Attempts to effect double dehydrobromination with $LiF–Li_2CO_3$-powered soft glass in HMPA[19] at 20° gave no reaction, even after 6 days.

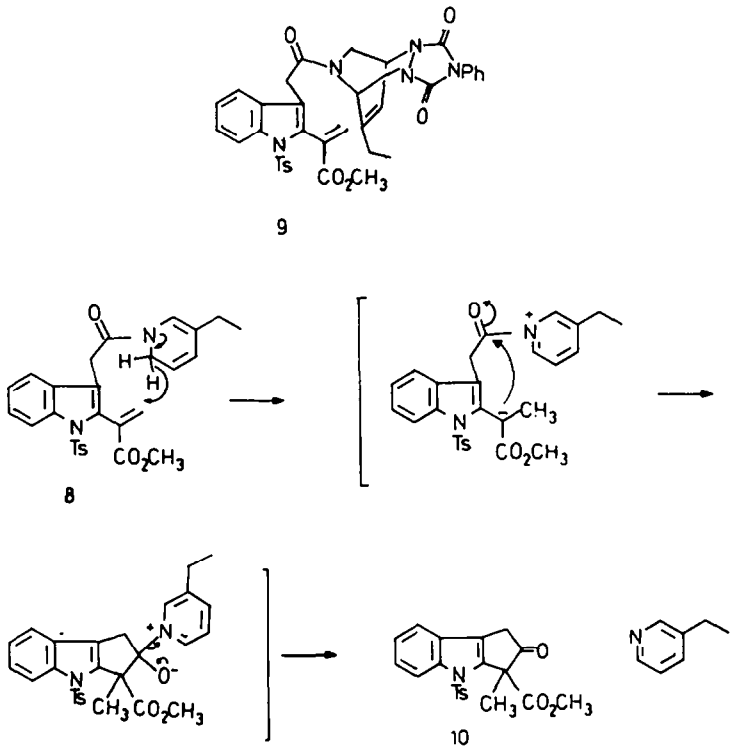
We now wish to report that the reaction of dibromide **7** with excess ethyl aluminum dichloride in HMPA at 20° results in the regioselective formation of the N-acyl-dihydropyridine **8** in excellent yield under extremely mild conditions. Although the exact role of the ethyl aluminum dichloride in this process is not fully understood, it appears to be functioning as both a Lewis acid to assist in weakening the C–Br bonds toward heterolytic cleavage and as an acid scavenger[20] to consume the leberated HBR. In a control experiment in which the dibromide was dissolved in HMPA, no dehydrobromination occurred. In another experiment in which aluminum trichloride was used instead, some double dehydrobromination occurred, however, the reaction was not as facile or clean. We are currently examining this mild, nonbasic procedure for the dehydrohalogenation of other systems, and we believe that it may prove to be quite useful for certain base-sensitive compounds.

The N-acyl-dihydropyridine **8** proved to be stable under argon at 20° for several days, however, attempts to purify this compound by flash chromatography[21] on silica gel led to extensive decomposition. This was of little concern, however, since the product obtained from the double dehydrohalogenation reaction was more than 90% pure. In any case, it was deemed desirable to obtain a readily purifiable derivative of **8** for further characterization; thus, a sample of **8** was reacted with N-phenyl-triazoline-3,5-dione to provide the adduct **9** in 80% yield.

When a dilute solution of **8** was heated under argon in toluene at 110° or carbon tetrachloride at 77°, TLC indicated the disappearance of the spot corresponding to **8** and the appearance of a new, higher R_f spot over the course of several hours. This new compound was shown to be the tricyclic system



Scheme 1. (a) $PhCH_2Br$; $NaBH_4$. (b) $ClCO_2CH_3$. (c) MeLi, HCl, Et_3N, indole-3-glyoxyloyl chloride. (d) TsCl, Et_3N. (e) $NaBH_4$. (f) $CH_3OCH_2CH_2C(OCH_3)_3$, 2,4,6-trimethylbenzoic acid, Δ. (g) Br_2, $-78°$. (h) $EtAlCl_2$, HMPA.



10, rather than the pentacyclic compound **II**. A plausible mechanism for the transformation of **8** to **10** involves an intramolecular hydride transfer to form an N-acyl-pyridinium intermediate which contains an ester enolate capable of undergoing Dieckmann condensation with accompanying loss of 3-ethylpyridine. The formation of 3-ethylpyridine was indeed confirmed by gas chromatography in a subsequent experiment.

Although hydride transfers from N-alkyl-dihydropyridines are well known,[22,7] and have been postulated for related systems,[9] to the best of our knowledge, this is the first example of a hydride transfer from an N-acyl-dihydropyridine.[23] In addition, it is interesting that the β-keto ester **10** does not undergo cleavage reactions typical of such systems, presumably due to the mild conditions under which it is formed and the absence of good nucleophiles in the reaction medium.

The reluctance of **8** to undergo intramolecular cyclization, although it reacts rapidly with N-phenyltriazoline-3,5-dione in an intermolecular cycloaddition may be the result of several factors. Although the triazoline-3,5-dione is undoubtedly a better dieneophile than the acrylate moiety in **8**, Sundberg[5] has effected intermolecular cycloaddition of a related α-(indol-2-yl) acrylate with an N-carboalkoxy-dihydropyridine. The inability of **8** to adopt a conformation suitable for intramolecular cycloaddition due to the constraints imposed by the amide linkage may be a more significant factor.

We are currently continuing our investigations concerning the synthesis of *Aspidosperma* and *Iboga* alkaloids.

EXPERIMENTAL

M.ps were obtained by using a Mel-Temp apparatus and are uncorrected. B.ps are uncorrected. Elemental analyses were performed by Canadian Microanalytical Service, Ltd., Vancouver, B.C. IR spectra were obtained on a Beckman Acculab 4 and are reported in cm $^{-1}$. NMR spectra were recorded on a Varian EM-360L (60 MHz) instrument; chemical shifts are reported in ppm downfield from TMS. Mass spectra were determined on a VG7070 GC/MS and associated VG2035 F/B Data System.

For experiments requiring dry solvents, ether and THF were distilled from Na/benzophenone. Benzene, methylene chloride, HMPA and toluene were distilled from calcium hydride. All reactions were conducted under a positive pressure of argon.

1-Benzyl-3-ethyl-1,2,5,6-tetrahydropyridine (**1**). A mixture of 3-ethylpyridine (29.7 g, 319 mmol) and benzyl chloride (40.7 g, 320 mmol) was left standing at 20° for 3 days. The resulting white solid product was powdered, washed with ether, then dried under vacuum in a dessicator to give 70.1 g (99%) of 1-benzyl-3-ethylpyridinium chloride which was used directly in the next step.

To a suspension of $NaBH_4$ (2.38 g, 68.4 mmol) in 60 ml of absolute EtOH at 0° was added dropwise a soln of 1-benzyl-3-ethylpyridinium chloride (4.00 g, 17.1 mmol) in 25 ml absolute EtOH over 15 min. When the addition was complete, the mixture was stirred at 0° for 3 hr, the cooling bath was removed, and the mixture allowed to warm to 20° for 21 hr. The EtOH was removed *in vacuo*, H_2O was added to dissolve the salts, then the aqueous phase was extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to give 3.43 g of **1** as a light yellow oil: b.p. 150° (0.1 mm). NMR and GCMS analysis showed **1** to be greater than 97% pure. NMR ($CDCl_3$): δ 7.32 (s, 5H), 5.4 (brs, 1H), 3.55 (s, 2H), 2.84 (d, J = 2 Hz, 2H), 2.6 – 2.3 (m, 2H), 2.3 – 1.6 (m, 4H), 0.97 (t, J = 7 Hz, 3H).

1-*Carbomethoxy*-3-*ethyl*-1,2,5,6-*tetrahydropyridine* (**2**). A soln of **1** (1.92 g, 9.54 mmol) and methyl chloroformate (1.5 ml, 19 mmol) in 20 ml benzene was heated at reflux for 5 hr. The benzene was removed *in vacuo*, and the remaining liquid was fractionally distilled through a 10 cm Vigreux column. The first fraction consisted of benzyl chloride: b.p. 32° (0.40 mm). The second fraction provided 1.34 g (83%) of **2**: b.p. 77° (0.40 mm). NMR ($CDCl_3$): δ 5.45 (brs, 1H), 3.7 (d, J = 2 Hz, 2H), 3.6 (s, 3H), 3.4 (t, J = 6 Hz, 2H), 2.3 – 1.7 (m, 4H), 1.0 (t, J = 7 Hz, 3H).

Indol-3-*ylglyox*(1,2,5,6-*tetrahydro*-3-*ethylpyridine*)*amide* (**3**). To a soln of MeLi (190 ml of a 1.4 M sol., 266 mmol) in 200 ml dry Et_2O at 0° was added dropwise a soln of **2** (16.13 g, 88.1 mmol) in 60 ml dry Et_2O over 17 min. The soln was stirred for 5 min and a soln of HCl gas (273 mmol) in 50 ml dry Et_2O was added dropwise over 15 min. The soln was stirred another 5 min, then a soln of NEt_3 (19.0 ml, 137 mmol) in 20 ml dry Et_2O was added dropwise over 10 min. Freshly prepared, finely powdered indole-3-glyoxyloyl chloride[24] (18.50 g, 89.4 mmol) was then added portionwise over 40 min and the resulting mixture stirred at 0° for 1 hr. Water (300 ml) was added and the mixture was stirred while warming to 20° until the salts were dissolved. The Et_2O layer was separated and the aqueous layer extracted with Et_2O. The combined Et_2O layers were washed with sat. $NaHCO_3$aq, then with 0.2 M pH 2 phosphate buffer, treated with activated C and $MgSO_4$, filtered and evaporated under reduced pressure to give 23.15 g (93%) of **3** as a light yellow foam of sufficient purity to use in the next step. IR (CH_2Cl): 3440, 1645, 1635, 1530, 1125 cm^{-1} NMR ($CDCl_3$): δ 11.2 (brs, 1H)M 8.5 – 8.1 (m, 1H), 7.7 (d, J = 3 Hz, 1H), 7.4 – 7.0 (m, 3H), 5.45 (brs, 1H), 4.1 (brs) and 3.8 (m) and 3.4 (m) (total 4H), 2.3 – 1.6 (m, 4H), 1.3 – 0.7 (m, 3H). An analytical sample was prepared by crystallization from EtOH: m.p. 120–122°. (Found: C 72.00%, H 6.37%, N 9.98%. Calc. for $C_{17}H_{18}N_2O_2$: C 72.32%, H 6.42%, N 9.92%).

1-*Tosylindol*-3-*ylglyox*(1,2,5,6-*tetrahydro*-3-*ethylpyridine*)*amide* (**4**). To a soln of **3** (5.10 g, 18.1 mmol) and tosyl chloride (3.5 g, 18.4 mmol) in 100 ml dry CH_2Cl_2 cooled to 0° was added NEt_3 (2.60 ml, 18.7 mmol). The mixture was stirred at 20° for 2 days. It was then washed with 10% HCl aq, and the aqueous wash was reextracted with CH_2Cl_2. The combined CH_2Cl_2 layers were dried ($MgSO_4$), the CH_2Cl_2 was removed *in vacuo*, and the residue was purified by chromatography on neutral alumina to give 7.51 g (95%) of **4** as a light yellow powder. IR (CH_2Cl_2): 1660, 1640, 1540, 1450, 1390, 1180 cm^{-1}. NMR ($CDCl_3$): δ 8.5 (s) and 8.4 (m) (total 2H), 8.1 – 7.7 (m, 3H), 7.5 – 7.1 (m, 4H), 5.5 (brs, 1H), 4.1 (brs) and 3.8 (m) and 3.4 (m) (total 4H), 2.4 – 1.7 (m) and 2.3 (s) (total 7H), 1.2–0.7 (m, 3H). An analytical sample was prepared by crystallization from ether: m.p. 114–116°. (Found: C 65.64%, H 5.84%, N 6.37%, S 7.33%. Calc. for $C_{24}H_{24}N_2O_4S$: C 66.04%, H 5.54%, N 6.42%, S 7.34%).

1 - *Tosylindol* - 3 - *ylglycol*(1,2,5,6 - *tetrahydro* - 3 - *ethylpyridine*)*amide* (**5**). To a soln of **4** (7.50 g, 17.2 mmol) in 1 : 1 anhydrous THF/MeOH (80 ml) at 20° was added rapidly solid $NaBH_4$ (0.60 g, 17.2 mmol). The mixture was stirred for 5 min and then NH_4Cl (3.7 g, 69 mmol) in 80 ml water was added. The THF/MeOH was removed under reduced pressure, then the aqueous phase was extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to give 7.33 g (97%) of **5** as a white foam which was used directly in the next step. IR (CH_2Cl_2): 3400, 2970, 1650, 1460, 1380, 1180 cm^{-1}. NMR ($CDCl_3$): δ 8.1 – 6.8 (m, 9H), 5.46 (d, J = 7 Hz) and 5.4 (brs) (total 2H), 4.63 (d, J = 7 Hz, 1H), 4.0 (brs) and 3.7 (m) and 3.2 (m) (total 4H), 2.4 – 1.4 (m) and 2.32 (s) (total 7H), 0.6 – 1.2 (m, 3H) High Res. Mass Spec: (Found: 438.1589. Calc. for $C_{24}H_{26}N_2O_4S$: 438.1611).

Methyl α - [1 - *tosylindol* - 3 - *acetic*(1,2,5,6 - *tetrahydro* - 3 - *ethylpyridine*)*amide* - 2 - *yl*] *acrylate* (**6**). A soln of **5** (4.19 g, 9.56 mmol), and 2,4,6-trimethyl benzoic acid (1.18 g, 7.20 mmol) in 28 ml (188 mmol) trimethyl 3-methoxyorthopropionate[15] was heated at 185° in a round-bottom flask topped with a Vigreux column and short-path distillation head for 3 hr. The excess ortho ester was removed *in vacuo* (0.1 mm), and residue was dissolved in 25 ml CH_2Cl_2 and stirred with 25 ml 5% HCl aq for 15 min. The CH_2Cl_2 layer was separated, dried ($MgSO_4$), and the CH_2Cl_2 was evaporated *in vacuo*. The residue was purified by flash chromatography[21] (Et_2O), followed by crystallization from Et_2O to give 3.50 g (72%) of **6** as colorless crystals: m.p. 153–154°. IR (CH_2Cl_2): 1740, 1650, 1610, 1460, 1380, 1180 cm^{-1}. NMR ($CDCl_3$): δ 8.3 – 8.0 (m, 1H), 7.8 – 6.95 (m, 7H), 6.72 (d, J = 2 Hz, 1H), 5.82 (d, J = 2 Hz, 1H), 5.45 (brs, 1H), 3.77 (s) and 4.0 – 3.2 (m) (total 9H), 2.4 – 1.6 (m) and 2.22 (s) (total 7H), 0.97 (t, J = 7 Hz, 3H). (Found: C 66.12%, H 5.84%, N 5.49%, S 6.45%. Calc. for $C_{28}H_{30}N_2O_5S$: C 66.38%, H 5.97%, N 5.53%, S 6.33%).

Methyl α - [1 - *tosylindol* - 3 - *acetic*(*trans* - 3,4 - *dibromo* - 3 - *ethylpiperidine*)*amide* - 2 - *yl*] *acrylate* (**7**). To a soln of **6** (0.475 g, 0.938 mmol) in 8 ml dry CH_2Cl_2 cooled to −78° was added dropwise a soln of Br_2 (0.050 ml, 0.156 g) in 5 ml dry CH_2Cl_2 over 15 min. The solution was stirred for 5 min, and the CH_2Cl_2 was removed *in vacuo*. The residue was purified by flash chromatography (95 : 5 CH_2Cl_2/EtOAc), followed by crystallization from ether–EtOH to give 0.584 g (93%) of **7** as colorless crystals: m.p. 159–160°. IR (CH_2Cl_2): 1740, 1665, 1450, 1380, 1185 cm^{-1}. NMR ($CDCl_3$): δ 8.3 – 8.0 (m, 1H), 7.7 – 7.0 (m, 7H), 6.7 (d, J = 2 Hz, 1H), 5.8 (d, J = 2 Hz, 1H), 4.8 – 4.4 (m, 2H), 3.8 (s) and 3.9 – 2.8 (m) (total 8H), 2.27 (s, 3H), 2.1 – 1.65 (m, 4H), 1.1 (t, J = 7 Hz, 3H).

5-*Oxo*-N_a-14,21-*dehydrosecodine* (**8**). To a soln of **7** (0.430 g, 0.646 mmol) in 10 ml anhyd HMPA at 20° was added 2.20 ml (3.90 mmol) of a 25% soln of $EtAlCl_2$ in hexane. The solution was stirred at 20° for 24 hr, cooled to 0°, and quenched by the slow addition of 10 ml water which caused a white solid to precipitate. Sufficient CH_2Cl_2 (3 ml) was added to redissolve the solid, then the soln was extracted twice with Et_2O. The combined Et_2O layers were washed 3 times with water, dried ($MgSO_4$), and the solvents were removed *in vacuo* to give 0.3220 g (99%) of crude **8** as an off-white solid. Further purification of **8** was not possible and the compound was used immediately in other reactions. IR (CH_2Cl_2): 1740, 1660, 1605, 1380, 1180, 915, 820 cm^{-1}. NMR ($CDCl_3$): δ 8.3 – 8.05 (m, 1H), 7.75 – 7.0 (m, 7H), 6.72 (d, J = 2 Hz, 1H), 6.3 (brs, 1H), 5.9 – 5.6 (m, 3H), 4.4 – 4.1 (m, 2H), 3.8 (s, 3H), 3.65. (brs, 2H), 2.2 – 1.75 (m) and 2.26 (s) (total 5H), 1.0 (t, J = 7 Hz, 3H). High Res. Mass spec. (from crude product): (Found: 504.1688. Calc. for $C_{28}H_{28}N_2O_5S$: 504.1718). Also shown in M.S. are peaks for **10** (397) and 3-ethylpyridine (107) in addition to major peaks at *m/e* 338, 242, 214, 154 which were also characteristic of **10**.

Diels–Alder adduct (**9**). To a soln of **8** (0.3220 g, 0.639 mmol) in 5 ml CH_2Cl_2 at 20° was added a soln of N-phenyl-triazoline-3,5-dione (0.1127 g, 0.644 mmol) in 5 ml CH_2Cl_2. The solution was stirred for 5 min and the CH_2Cl_2 was removed *in vacuo*. The residue was purified by flash chromatography (Et_2O), followed by crystallization from ether–EtOH to give 0.347 g (80%) of **9** as colorless crystals: m.p. 182–184°. IR (CH_2Cl_2): 1780, 1730, 1675, 1400, 1390, 1180, 920, 820 cm^{-1}. NMR ($CDCl_3$): 8.3 – 8.0 (m, 1H), 7.8 – 7.0 (m, 12H), 6.8 (d, J = 2 Hz, 1H), 6.7 (d, J = 2 Hz, 1H), 6.05 (brs, 1H), 5.8 (d, J = 2 Hz, 1H), 5.1 – 4.85 (m, 1H), 3.95 – 3.05 (m) and 3.82 (s) (total 7H), 2.4 – 1.5 (m) and 2.28 (s) (total 5H), 1.2 – 0.7 (m, 3H). High Res. Mass Spec. (CI): (Found: 680.2167. Calc. for $C_{36}H_{33}N_5O_5S$: for M + 1 680.2176). Also Found: 679.2045. Calc. for M 679.2096. The mass spec. also shows a base peak corresponding to M + 1 for **8**; (Found: 505.1757. Calc. for $C_{28}H_{29}N_2O_5S$. 505.1794). Also present is a peak corresponding to M for **8**; (Found: 504.1713. Calc. for $C_{28}H_{28}N_2O_5S$: 504.1718).

2 - *Oxo* - 3 - *methyl* - 3 - *carbomethoxy* - 4 - *tosyl* -

cyclopent[b]*indole* (**10**). A soln of crude **8** (0.040 g, 0.080 mmol) in 5 ml toluene was heated at reflux under argon for 21 hr. The toluene was removed *in vacuo*, and the residue was purified by flash chromatography (Et_2O) to give 0.0151 g (47%) of **10** as a viscous, colorless liquid. IR (CH_2Cl_2): 1780, 1750, 1730, 1375, 1180, 915 cm^{-1}, NMR ($CDCl_3$): 8.0 – 7.1 (m, 8H), 3.7 (s, 3H), 3.55 (s, 2H), 2.33 (s, 3H), 1.8 (s, 3H). High resolution mass spec. (Found: 397.0999. Calc. for $C_{21}H_{19}NO_5S$: 397.0984).

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