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# CHEMISTRY OF INDOLES CARRYING A BASIC FUNCTION. PART IX.[1] UNEXPECTED CYCLIZATIONS OF DIKETONES DERIVED FROM UHLE'S KETONE[#]

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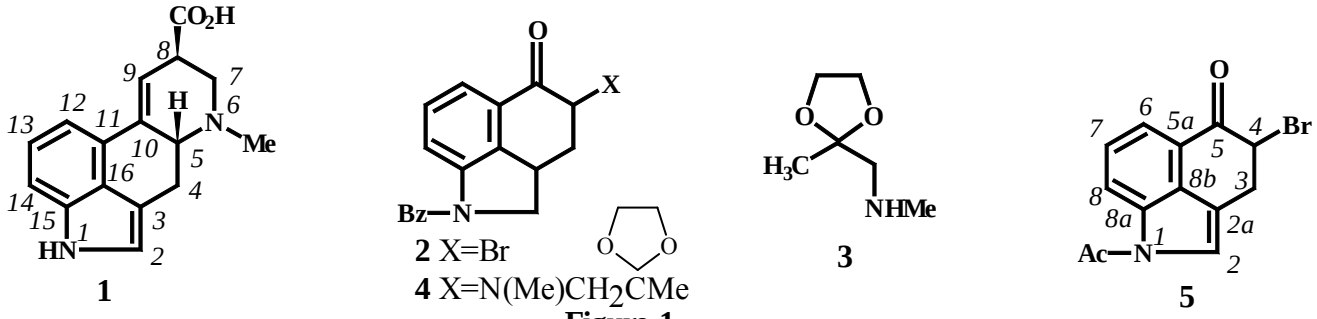
[#]*We dedicate this paper to Professor Pierre Potier on the occasion of his 70th birthday.*

***Abstract*** – Starting from a tricyclic diketone (**14**) obtained by Bowman's method, a tetracyclic oxonaphthalene derivative (**17**) has been prepared through intramolecular aldol condensation followed by indole → naphthalene isomerization. An unexpected formation of a lactol ether (**16**) was observed as a result of acidic treatment of **14**. Two modified reaction sequences starting from *N*-methyl derivatives have also been presented. The keto ketal (**26**) gave a macrocyclic lactol (**27**) with unexpected structure as a result of deketalization with trimethylsilyl iodide. The formation of a tetracyclic lactam (**37**) was observed while applying the modified Reformatsky reaction to ketone (**33**).

About two decades after the first successful synthesis of racemic lysergic acid (**1**; Figure 1) by the Woodward-Kornfeld group,[2] Bowman and co-workers tried to adopt the key elements of the results of this legendary American cooperation. Their experiments[3] supplied two instructive facts. While the 4-bromo derivative of the so-called Kornfeld's ketone (**2**) reacts smoothly with methylaminoacetone ethylene ketal (**3**) yielding a tertiary amine (**4**, 71 %),[2] the corresponding indole derivative (*e.g.* 1-acetyl-4-bromo-Uhle ketone; **5**) did not afford any basic material using the same reaction conditions.[3d]

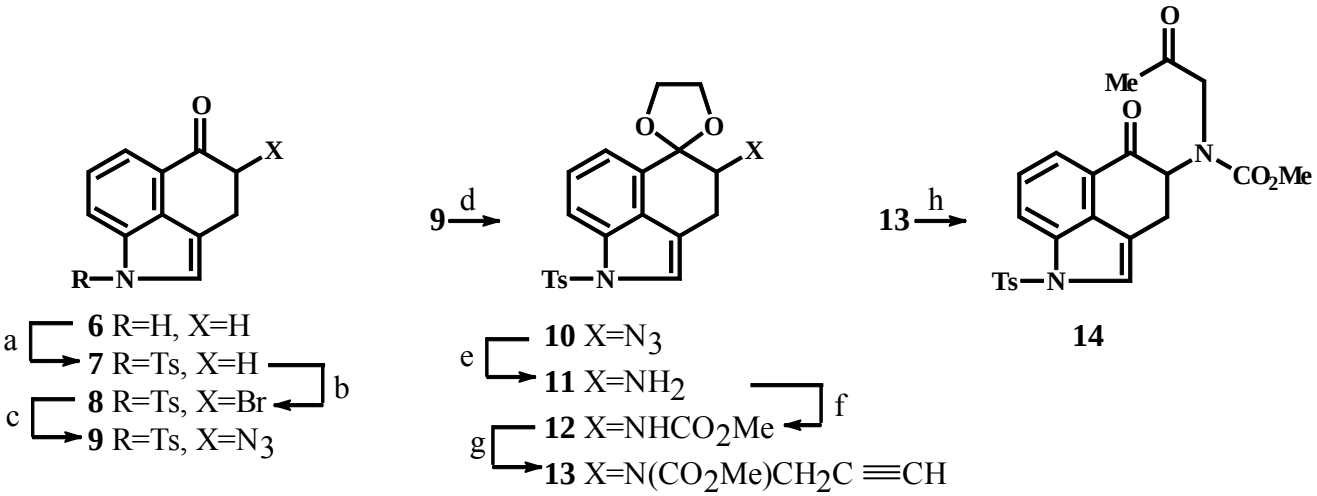



**1** **2** X=Br **3** **5**

**4** X=N(Me)$CH_2CMe$

**Figure 1**

On the other hand, they finally succeeded in synthesizing a tricyclic diketone with an urethane group (**14**, Scheme 1) by applying a longer but fruitful route. Compound (**14**) would be suitable for an intramolecular aldol condensation leading to a tetracyclic α,β-unsaturated ketone but the cyclization step failed.




a → **6** R=H, X=H

a → **7** R=Ts, X=H; b → **8** R=Ts, X=Br

c → **9** R=Ts, X=$N_3$

**9** —d→ **10** X=$N_3$

e → **11** X=$NH_2$; f → **12** X=$NHCO_2Me$

g → **13** X=$N(CO_2Me)CH_2C{\equiv}CH$

**13** —h→ **14**

**Scheme 1** -- ***reagents and conditions*: a) KOH/TsCl, TBAHS, $CH_2Cl_2$, 0 °C → rt, 1.5 h, 91 %; b) $Br_2$-1,4-dioxane, $CCl_4$+$CHCl_3$+$Et_2O$, 5-10 °C, 3 h, 77 %; c) $NaN_3$, DMF+$H_2O$+$MeCO_2H$, 5 °C → rt, 0.5 h, 88 %; d) ethylene glycol, $CHCl_3$, $BF_3{\cdot}Et_2O$, rt, 28 h, 95 %; e) LAH, THF, 0 °C → rt, 3 h, 97 %; f) $ClCO_2Me$, THF+$H_2O$+$NaHCO_3$, 5-10 °C, 0.5 h, 72 %; g) 1: NaH, benzene+DMF, rt, 1 h, 2: propargyl bromide, rt, 24 h, 68 %; h) 2.5 N $H_2SO_4$, dioxane, $HgSO_4$, 1 h, 90 °C, 98 %.**

TsCl=4-toluenesulfonyl chloride; TBAHS=tetra-*n*-butylammonium hydrogen sulfate

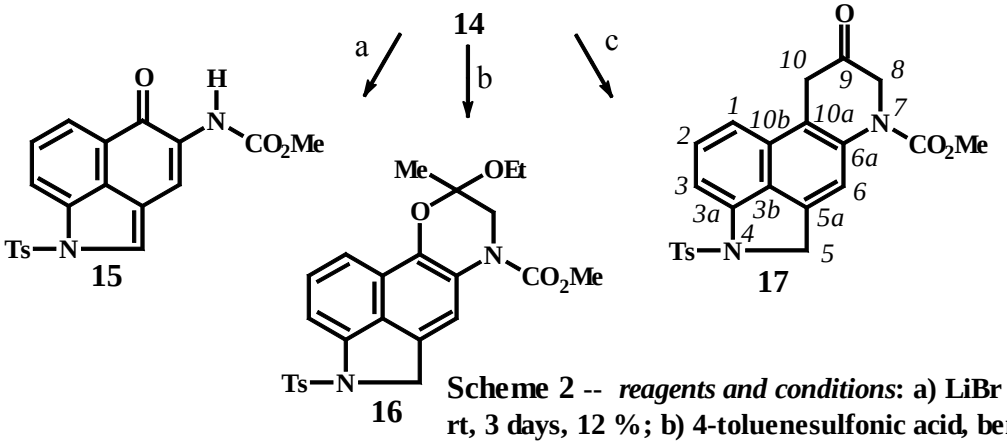
While working on the total synthesis of **1** *via* an 8-oxo-derivative,[1] we also prepared **14** hoping to find a reagent for the ring closure, and at the same time to modify the original pathway (*e.g.* to synthesize *N*-methyl derivatives instead of urethanes).

Scheme 1 depicts Bowman's approach which was carried out with a few modifications as described in the EXPERIMENTAL. Uhle's ketone (**6**)[4] was protected as *N*-tosyl derivative using the combination of Illi[5] and Kikugawa's procedure[6] for *N*-sulfonylation of indoles. The *N*-protected ketone (**7**)[7] was treated with bromine-1,4-dioxane to yield α-bromo ketone (**8**). Bromine→azide exchange was performed with $NaN_3$, and the carbonyl function of **9** was protected as ethylene ketal (**10**). Reduction of azide (**10**) with LAH

supplied amine (**11**) which was allowed to react with methyl chloroformate to afford urethane (**12**). (In the $^1$H NMR spectra of compounds (**12-14**), a characteristic duplication of the signals was observed at room temperature due to the hindered rotation of the amide group. By elevating the temperature those signals undergo coalescence and subsequent signal sharpening). The sodium salt of **12** was alkylated with propargyl bromide into an acetylene derivative (**13**). Classical Kucherov reaction (aqueous $H_2SO_4$, $HgSO_4$) transformed the acetylene side chain into an acetonyl group, and at the same time the carbonyl function was regenerated in the acidic solution to afford diketone (**14**).

The intramolecular aldol condensation between two ketones, the aldolization-dehydration process, is widely used to prepare cyclic α,β-unsaturated ketones.[8] About half thousand examples can be found in the Beilstein on-line system, and this commonly used step was applied in several sophisticated total syntheses of natural products.[9] However, the aldol condensation of ketones leading to substituted piperidines is a rather unique transformation. In the literature only four reagents were found to perform such application: NaOMe in EtOH,[2] PPA in nitromethane,[10] aq. $H_2SO_4$,[11] LiBr and triethylamine in THF.[12]

In order to obtain a tetracyclic ketone starting from **14** by intramolecular aldol condensation, several metal alkoxides (NaOMe, NaOEt, *tert*-BuOK in several types of solvents) were tried unsuccessfully in accordance with Bowman's examinations as verified by *Novartis* researchers.[12] Other bases (LHMDS, LDA, *n*-BuLi and *t*-BuOK) gave unsuccessful reactions too.

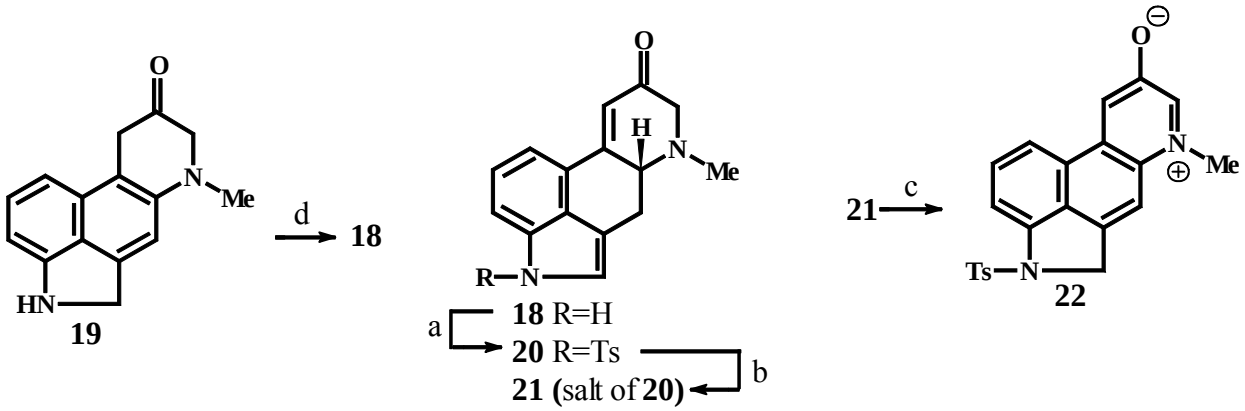



**Scheme 2** -- ***reagents and conditions*: a) LiBr + TEA, THF, rt, 3 days, 12 %; b) 4-toluenesulfonic acid, benzene, refl, 2 h, 41 %; c) KF/$Al_2O_3$(b), benzene, refl, 2 h, 63 %.** TEA=triethylamine

While using LiBr as a reagent, in addition to the starting material only an oxidized compound (**15**) (Scheme 2) was obtained in a low yield, when the reaction mixture was allowed to react for 3 days at room temperature. (A similar carbon-nitrogen bond cleavage in urethanes has already been described in our earlier examinations).[13] On boiling a solution of **14** (benzene, 2 h) in the presence of 4-toluenesulfonic acid,[14] a totally unexpected lactol ether (**16**) was formed (41 % yield). The formation of lactols is an undesirable side reaction of diketones of indoline derivatives[2,10] but the ether part of **16** is a new speciality. (It turned out that the ethoxy group stems from the ethanol content of the chloroform used

as solvent for chromatographic purification). The indole → naphthalene isomerization *via* migration of double bonds under strong acidic conditions is a well known characteristic of lysergic acid derivatives.[15] Since we successfully used $KF/Al_2O_3$ as base in a cyclization step in the course of our enantioselective synthesis of epibatidine,[16] **14** was allowed to react with KF on basic $Al_2O_3$[17] in benzene resulting in a tetracyclic ketone (**17**). The formation of ring D and the rearrangement of rings B and C is evidenced by the NMR spectroscopic experiments. The H-10 methylene protons gave NOE with H-1, while the protons of the other methylene group (H-5) gave NOE with the aromatic proton at 7.5 ppm (H-6). Moreover, the long-range heterocorrelation of the H-10 protons with the quaternary carbons of ring C also corroborate the tetracyclic ketone structure proposed for **17**.

It is worth mentioning that KF on neutral $Al_2O_3$ or the basic $Al_2O_3$ without KF did not afford the cyclized product, though $Al_2O_3$ may also serve as an excellent reagent for the aldol condensation.[18] The structure (**17**) indicates that we first succeeded in constructing the desired bond starting from diketone in the indole series, but unfortunately migration of the double bonds vitiates the value of this result.




**Scheme 3** -- ***reagents and conditions*: a) KOH/TsCl, TBAHS, $CH_2Cl_2$, 0 °C → rt, 2 h, 66 %; b) DMSO-$d_6$+$CF_3CO_2D$, rt, 5 min; c) after 4-5 weeks; d) ref. 19.**

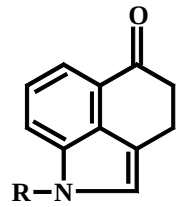
Moreover, the structure (**17**) contradicts the simple molecular orbital calculations.[15,19] While the π-electron system of **1** is transformed to the more stable naphthalene system and the isomerization is essentially irreversible in an acid catalysed process, in the case of 8-oxo derivatives (**18**, **19**; Scheme 3) the position of this equilibrium is expected to be reversed and therefore ketonaphthalene (**19**) might be convertible to 8-oxoergolene (**18**) by isomerization. The cited calculations on **18** and **19** suggest that this isomerization might succeed, the resonance energy of **18** favors it to the ketonaphthalene (**19**) by 0.136β. This hypothesis initiated an approach to synthesize **18** *via* **19** in the hope that ketoergolene (**18**) should be a useful precursor to synthesise **1**. To verify these simple calculations and hypotheses a few experiments were performed, the final synthetic version, however, has never been published.

We tried to find some experimental proof for the last mentioned equilibrium. 8-Oxoergolene (**18**, prepared by degradation of **1** by using Bernardi's method)[20] was transformed into *N*-tosyl derivative (**20**,[21] 66 %). The transformation of **20** was examined in an NMR tube (DMSO-$d_6$; acid catalyst: $CF_3CO_2D$) for about 4-5 weeks at room temperature. The spectra were run about twenty times during this period. The first spectra ($^1H$, $^{13}C$) showed a well-defined ionic compound (**21**) which was transformed gradually into a betaine (**22**) nearly as the only product. (This betaine-like structure has been known in the dihydroindole series for a long time and the formation of the pyridyl ring was interpreted by a simple oxidation step).[2]

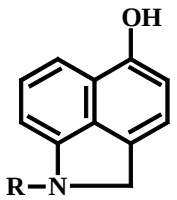
The tetracyclic ketone structures of both **20** and **21** follow from the NOE connectivities of the H-9 and H-12 protons. The downfield shifts of the *N*-Me, H-7 and H-5 protons of **21** in comparison with those of **20** reflect the presence of a charged system.

Later, we have performed more sophisticated semiempirical[22a] and *ab initio*[22b] calculations (Table 1) which were in contradiction with the result of the simple molecular orbital calculation of Anselmi on the structures (**18** and **19**)[19] and may explain the experimental results.

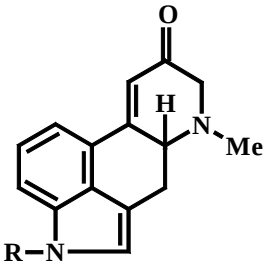
**Table 1.** Calculated total energy differences for indole – naphthalene isomers



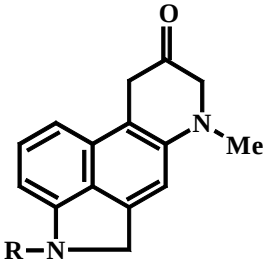

**6** R=H
**Ac-6** R=Ac




**6'** R=H
**Ac-6'** R=Ac



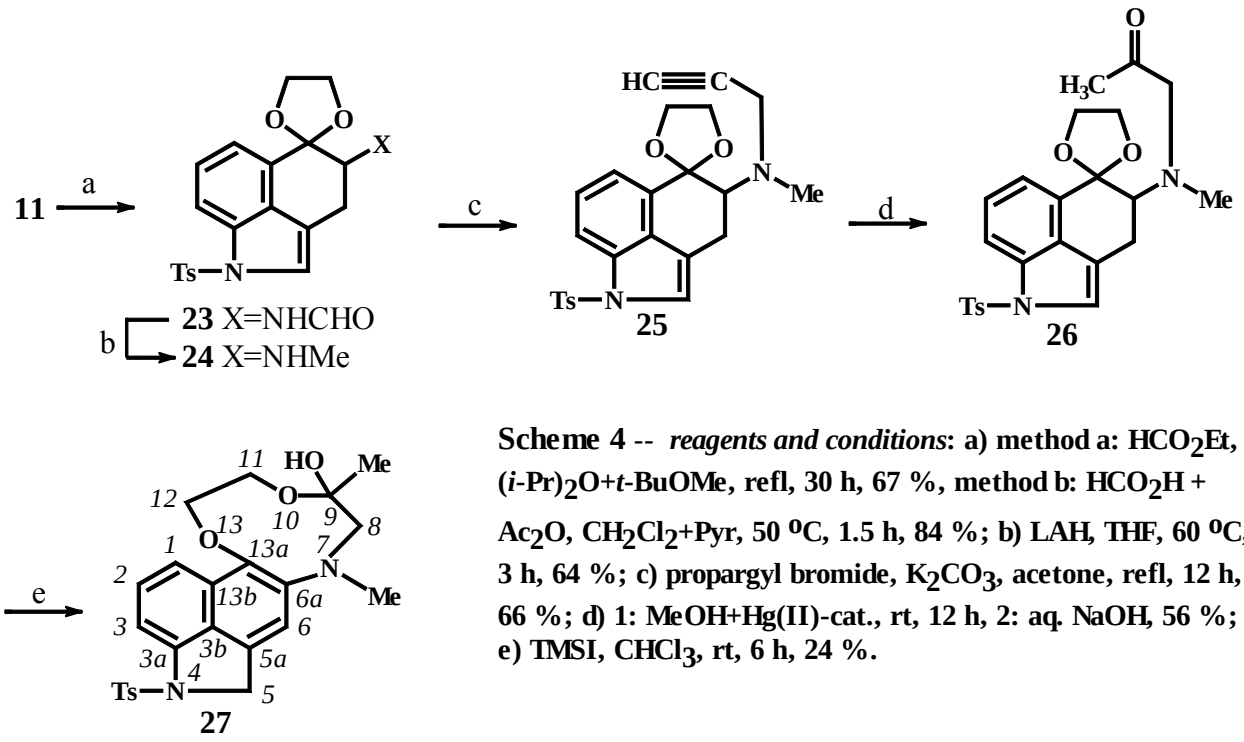

**18** R=H
**Ac-18** R=Ac




**19** R=H
**Ac-19** R=Ac

| Method | $E_6$-$E_{6'}$ [kJ/mol] | $E_{Ac\text{-}6}$-$E_{Ac\text{-}6'}$ [kJ/mol] | $E_{18}$-$E_{19}$ [kJ/mol] | $E_{18}$-$E_{19}$ [kJ/mol] |
|---|---|---|---|---|
| PM3 [22a] | -8.8 | 8.3 | 63 | 60 |
| 6-31G [22b] | -7.9 | 11.7 | 50 | 66 |

Although in the case of the oxo indole (**6**) – hydroxynaphthol (**6'**) isomers the oxoindole structure (**6**) was calculated as about 8 kJ/mol more stable, the calculated stability reversed even for their *N*-acetylated derivatives (**Ac-6**) and (**Ac-6'**), the later being about 10 kJ/mol more stable. The calculations on the 8-oxoergolene (**18**) – ketonaphthalene (**19**) isomers and their acetylated forms (**Ac-18** and **Ac-19**) revealed that the naphthalene isomers (**19** and **Ac-19**) are about 60 kJ/mol more stable than the corresponding indole isomer (**18** or **Ac-18**). These results agree with the experimentally detected formation of **17** and **22** containing the more stable naphthalene skeleton as well.




**Scheme 4** -- ***reagents and conditions*: a) method a: $HCO_2Et$, ($i$-Pr)$_2O$+$t$-BuOMe, refl, 30 h, 67 %, method b: $HCO_2H$ + $Ac_2O$, $CH_2Cl_2$+Pyr, 50 °C, 1.5 h, 84 %; b) LAH, THF, 60 °C, 3 h, 64 %; c) propargyl bromide, $K_2CO_3$, acetone, refl, 12 h, 66 %; d) 1: MeOH+Hg(II)-cat., rt, 12 h, 2: aq. NaOH, 56 %; e) TMSI, $CHCl_3$, rt, 6 h, 24 %.**

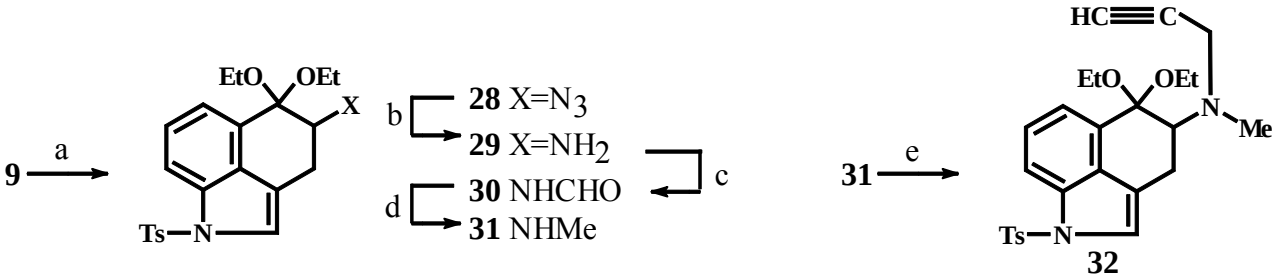
Our modified version of Bowman's approach to the required ergolene skeleton involves preparing *N*-methyl derivatives instead of urethanes (Scheme 4).

To this end it has been necessary to reserve the main elements of the original route, and to find an optimal embranchment into *N*-methyl analogs. To obtain this type of compounds, first the ketal amine (**11**) was formylated (method a: ethyl formate; method b: mixed anhydride from formic acid and acetic anhydride) into amide (**23**), then in a subsequent step the formyl group was reduced with LAH into a methyl group to afford a secondary amine (**24**). While the alkylation of **24** with propargyl bromide was performed smoothly into the desired tertiary amine (**25**), the reagent of the classical Kucherov reaction (aq. $H_2SO_4$, $HgSO_4$), which afforded **14** in excellent yield (Scheme 1), gave an inseparable tar in this case. However, a modified reaction[23] (acid catalysed methanol addition in the first step followed by basic hydrolysis of the obtained enol ether) supplied the ketal ketone (**26**). To obtain a diketone, only a trivial step remained to be solved: regeneration of the ketone at C5. About a dozen commonly used procedures were tried without any success. (Other examples were found to describe the difficulty of hydrolysing ketals in the neighbourhood of a basic nitrogen atom in the earlier publications).[2,10] Only trimethylsilyl iodide[24] gave a well-defined but unexpected product. A macrocyclic lactol with a naphthalene ring (**27**) was isolated in a moderate yield. (Diiodosilane,[25] recommended as a reagent for a mild and efficient cleavage of ketals, gave **27** only in traces beside the starting material).

The formation of the new heteroring followed from the chemical shifts of C and D ring carbons, and from the NOEs of the H-1 and H-12 protons. Moreover, the C9-Me gave NOEs with the *N*-Me, H-8 and H-11

protons. In addition, the HRMS spectral data of **26** and **27** showed the same elemental composition but fully diverse fragmentation.

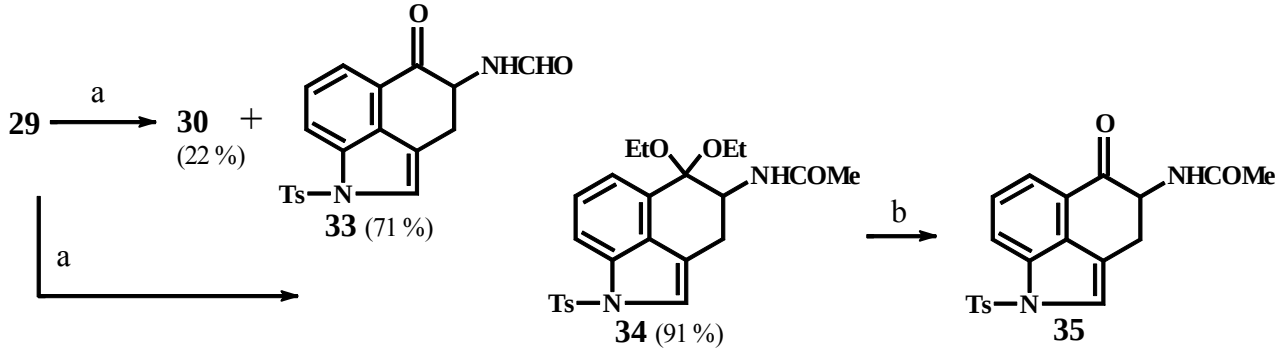
To avoid the above difficulties of deketalization at C5, a less stable protective group[26] (open-chain diethyl ketal) was chosen (Scheme 5).




**Scheme 5** -- ***reagents and conditions*: a) EtOH+$(EtO)_3CH$, $CHCl_3$, $BF_3{\cdot}Et_2O$, mol. sieve, rt, 24 h, 75 %; b) LAH, THF, 0 °C→rt, 3 h, 90 %; c) $HCO_2Et$, $(i\text{-}Pr)_2O$, 60 °C, 48 h, 84 %; d) LAH, THF, 60 °C, 2 h, 59 %; e) propargyl bromide, acetone, $K_2CO_3$, 60 °C, 12 h, 97 %.**

Azido ketone (**9**) was treated with ethanol in $CHCl_3$ in the presence of triethyl orthoformate, $BF_3{\cdot}Et_2O$ and molecular sieve (4 Å) to afford the ketal azide (**28**). Reduction of the azide group was performed with LAH again to yield amine (**29**). Formylation of **29** was accomplished by treatment with ethyl formate resulting in the *N*-formyl derivative (**30**). The secondary amine (**31**) was obtained by reduction, then amine (**31**) was alkylated with propargyl bromide into tertiary amine (**32**). Unfortunately, the synthesis of **32** proved to be the terminal point of this modified approach. Neither the classical Kucherov reagent (addition of water), nor the modified version (addition of methanol, hydrolysis), which was suitable to prepare **14** or **26**, or other variations (application of aniline[27] or formic acid[28]) gave the desired diketone or a ketal.

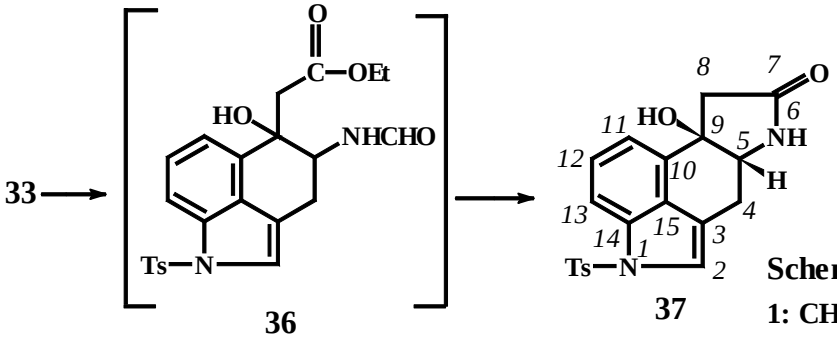
In connection with the preparation of formyl ketal (**30**), it is worth mentioning that only the application of ethyl formate afforded a reproducible result. If the mixed anhydride method was used for the formylation of amine (**29**), sometimes the desired *N*-formylation, sometimes an undesired *N*-acetylation occurred in a fully random way.




**Scheme 6** -- ***reagents and conditions*: a) $HCO_2H$+$Ac_2O$, $CH_2Cl_2$+Pyr, rt, 1.5 h; b) HCl/$H_2O$, acetone, rt, 3 h, 86 %.**

In addition, the formylation gave compound (**30**) only as a minor product, whereas the main product was a deprotected *N*-formyl derivative (**33**). Sometimes the *N*-acetyl ketal (**34**) was formed exclusively in a nearly quantitative yield. The protective group of **34** could be removed by a mild acidic treatment to yield ketone (**35**, Scheme 6).

In the previous part of our series[1] a reaction sequence leading to the ergoline skeleton was presented, in which a modified Reformatsky reaction was one of the key steps. To examine the scope and limitations of this transformation, ketone (**33**) was allowed to react with ethyl acetate lithiated with LHMDS at –78 °C (Scheme 7). After acidification, a *cis*-annellated tetracyclic lactam (**37**) was obtained presumably *via* the hydroxy ester (**36**). The structure of **37** was elucidated by NMR spectral measurements. The NOE between H-5 and OH protons was determinant in defining the *cis*-annellation of rings C and D. In addition, H-5 showed NOE correlations with the H-4 and CONH protons, while irradiation of the OH resonance resulted in NOE on the H-8 protons.




**Scheme 7** -- ***reagents and conditions*:**
**1: $CH_3CO_2Et$+LHMDS, THF, -78 °C, 0.5 h,**
**2: $HCl/H_2O$, 24 %.**

Another approach to ergot derivatives will be presented shortly.

**Table II**. $^1$H NMR signals of C4-substituted Uhle's ketones ($CDCl_3$, rt, δ, ppm, *J* in Hz)

| | **7** | **8** | **9**[a] | **14**[b] | **33**[c] | **35**[d] |
|---|---|---|---|---|---|---|
| H-2 | 7.34(br s) | 7.49(1.7+0.8) | 7.75(1.8) | 7.37(2.0) | 7.38(2.0) | 7.38(2.0) |
| H-$3_A$ | 2.84(7.2) | 3.57 (17.5+3.6+0.8) | 3.10 (15.7+11.0+1.8) | 3.25 (15.6+12.6+2.0) | 2.89 (15.6+12.3+2.0) | 2.84 (15.5+12.2+2.0) |
| H-$3_B$ | | 3.79 (17.5+4.6+1.7) | 3.44(15.7+6.9) | 3.51 (15.6+6.9) | 3.96 (15.6+6.9) | 3.92 (15.5+6.8) |
| H-4 | 3.17(7.2) | 4.81(4.6+3.6) | 4.86(11.0+6.9) | 4.97(12.6+6.9) | 4.87 (12.3+6.9+5.3) | 4.85 (12.2+6.8+5.5) |
| H-6 | 7.69(7.6+0.5) | 7.77(7.6+0.8) | 7.67(7.4+0.5) | 7.70(7.7+0.6) | 7.68(7.6+0.5) | 7.68(7.6+0.6) |
| H-7 | 7.39(8.1+7.6) | 7.45(8.1+7.6) | 7.54(8.1+7.4) | 7.43(8.1+7.7) | 7.42(8.2+7.6) | 7.44(8.2+7.6) |
| H-8 | 8.09(8.1+0.5) | 8.13(8.1+0.8) | 8.16(8.1+0.5) | 8.11(8.1+0.6) | 8.12(8.2+0.5) | 8.14(8.2+0.6) |
| Ts-Me | 2.35(s) | 2.36(s) | 2.32(s) | 2.37(s) | 2.33(s) | 2.36(s) |
| Ts-*o*-CH | 7.76(m) | 7.78(m) | 7.91(m) | 7.76(m) | 7.76(m) | 7.77(m) |
| Ts-*m*-CH | 7.24(m) | 7.25(m) | 7.40(m) | 7.25(m) | 7.24(m) | 7.26(m) |
| Side chain | [a]in DMSO-$d_6$; [b]at 70 °C, COC$H_3$: 2.14(s), NC$H_2$: 3.95+4.30 ($J_{gem}$= 18.4), OC$H_3$: 3.88(s); [c]N*H*: 6.77 (5.3), C*H*O: 8.37(s); [d]N*H*: 6.69(5.5), COC$H_3$: 2.11(s). | | | | | |

**Table III**. $^{13}C$ NMR signals of C4-substituted Uhle's ketones ($CDCl_3$, rt, δ, ppm)

| | **7** | **8** | **9** | **14**[a] | **33**[b] | **35**[c] |
|---|---|---|---|---|---|---|
| C-2 | 121.61 | 123.63 | 122.77 | 120.19 | 122.76 | 122.64 |
| C-2a | 116.93 | 113.58 | 113.99 | 115.66+115.93 | 114.77 | 115.12 |
| C-3 | 20.36 | 31.18 | 27.27 | 26.26+26.96 | 27.68 | 27.79 |
| C-4 | 38.23 | 48.78 | 63.98 | 63.14+63.36 | 54.67 | 55.79 |
| C-5 | 196.59 | 188.75 | 191.89 | 192.65+193.07 | 193.16 | 193.89 |
| C-5a | 126.55 | 126.70 | 124.77 | 126.91+127.02 | 125.16 | 125.40 |
| C-6 | 119.11 | 121.21 | 120.36 | 122.58+122.69 | 119.83 | 119.70 |
| C-7 | 125.50 | 126.07 | 126.11 | 125.92+126.04 | 125.82 | 125.73 |
| C-8 | 118.47 | 119.19 | 119.24 | 119.23+119.28 | 119.36 | 119.20 |
| C-8a | 133.86 | 133.13 | 133.68 | 130.30 | 133.62 | 133.62 |
| C-8b | 135.17 | 133.68 | 133.80 | 133.90+134.03 | 133.84 | 133.87 |
| Ts-Me | 21.53 | 21.57 | 21.59 | 21.75 | 21.56 | 21.56 |
| Ts-C1' | 134.85 | 135.06 | 135.04 | 135.29 | 134.85 | 134.91 |
| Ts-*o*-CH | 126.70 | 126.77 | 126.79 | 126.07+126.13 | 126.68 | 126.68 |
| Ts-*m*-CH | 129.95 | 130.06 | 130.09 | 130.27 | 130.06 | 130.04 |
| Ts-*p*-C | 145.14 | 145.40 | 145.46 | 145.56 | 145.41 | 145.34 |
| Side chain | [a]$COCH_3$: 27.02+27.17, $OCH_3$: 53.36+53.41, $NCH_2$: 56.30+57.08, $CO_2$: 156.71+156.84, CO: 204.07+204.44; [b]NCO: 161.21; [c]$CH_3$: 23.27, NCO: 170.38. | | | | | |

## EXPERIMENTAL

Mps are uncorrected. MS spectra were run on an AEI-MS-902 (70 eV; direct insertion) and on a Kratos-MS-902 mass spectrometer. FAB-MS spectra were measured on a ZAB 2SEQ spectrometer. IR spectra were taken on a Nicolet 7795 FT-IR spectrophotometer. NMR spectroscopy measurements were carried out on a Varian Unity Inova (400 MHz for $^1H$ and 100 MHz for $^{13}C$) instrument. Chemical shifts are given relative to TMS=0.00 ppm. Elemental analyses (C, H, N, S) were carried out by Vario EL III (Elementar Analysen System Gmbh) automatic microanalyzer. For TLC analyses Merck aluminium sheets (silica gel 60 $F_{254}$) were used and visualized under UV light or developed by iodine atmosphere and immersion in a solution of *o*-tolidine. Preparative separations were performed by column chromatography on Merck Kieselgel 60 (0.063-0.200) and Merck Kieselgel 60 (0.040-0.063). Solvents were carefully dried and purified by appropriate methods. The reactions were carried out under nitrogen.

Semiempirical calculations (MNDO, AM1 and PM3) using the HyperChem[22a] and HF *ab initio* calculations (STO-3G, 3-21G and 6-31G) using the Gaussian 98[22b] program packages were performed on AMD Athlon 1800+/1 GB or 2600+/1 GB PC's running under Windows XP or Linux (RedHat 7.3).

**Table IV**. $^1$H NMR signals of C4-substituted Uhle's ketones as dioxolanes ($CDCl_3$, rt, δ, ppm, *J* in Hz)

| | **10** | **11**[a] | **12**[b] | **13**[c] | **23**[d] | **24**[e] | **25**[f] | **26**[g] |
|---|---|---|---|---|---|---|---|---|
| H-2 | 7.27 (1.4+1.3) | 7.24 (1.3+1.0) | 7.25 (br s) | 7.24 (1.8) | 7.24 (1.5) | 7.22 (1.4+1.2) | 7.22 (br s) | 7.21 (br s) |
| H-$3_A$ | 3.09 (15.9+8.3 +1.4) | 2.85 (15.8+8.1 +1.3) | 2.96 (15.6+7.5) | 3.21 (15.5+5.0) | 2.97 (16.1+8.3 +1.5) | 2.94 (15.3+5.7 +1.2) | 3.1-3.26 (m) | 3.1-3.25 (m) |
| H-$3_B$ | 3.21 (15.9+4.5 +1.3) | 3.16 (15.8+4.6 +1.0) | 3.20 (15.6+4.5) | 3.44 (15.5+11.5 +1.8) | 3.17 (16.1+5.3) | 3.14 (15.3+4.0 +1.4) | 3.1-3.26 (m) | 3.1-3.25 (m) |
| H-4 | 3.93 (8.3+4.5) | 3.30 (8.1+4.6) | 4.33 (9.5+7.5 +4.5) | 4.80 (11.5+5.0) | 4.60 (8.3+5.3 +4.7) | 3.08 (5.7+4.0) | 3.25 (10.4+4.4) | 3.13(m) |
| H-6 | 7.27 (7.3+0.7) | 7.22 (7.5+0.5) | 7.27 (7.4+0.7) | 7.18 (7.3+0.7) | 7.29 (7.5+0.8) | 7.21 (7.5+0.8) | 7.25 (7.5+0.5) | 7.23 (7.3+1.3) |
| H-7 | 7.35 (8.1+7.3) | 7.33 (8.2+7.5) | 7.34 (8.2+7.4) | 7.29 (8.2+7.3) | 7.31 (8.1+7.4) | 7.28 (8.1+7.5) | 7.32 (8.1+7.5) | 7.31 (8.1+7.3) |
| H-8 | 7.87 (8.1+0.7) | 7.86 (8.2+0.5) | 7.88 (8.2+0.7) | 7.86 (8.2+0.7) | 7.82 (8.1+0.8) | 7.72 (8.1+0.8) | 7.84 (8.1+0.5) | 7.82 (8.1+1.3) |
| Ts-Me | 2.33(s) | 2.35(s) | 2.37(s) | 2.37(s) | 2.35(s) | 2.33(s) | 2.33(s) | 2.34(s) |
| Ts-*o*-CH | 7.76(m) | 7.76(m) | 7.76(m) | 7.73(m) | 7.74(m) | 7.73(m) | 7.76(m) | 7.74(m) |
| Ts-*m*-CH | 7.22(m) | 7.24(m) | 7.22(m) | 7.20(m) | 7.26(m) | 7.19(m) | 7.21(m) | 7.21(m) |
| $O(CH_2)_2O$ | 4.2-4.6 (m) | 4.1-4.32 (m) | 4.15-4.4 (m) | 4.0-4.30 (m) | 4.08-4.25 (m) | 4.1-4.26 (m) | 4.05-4.30 (m) | 4.15-4.2 (m) |
| Side chain | [a]N*H*$_2$: 1.76 (br s); [b]N*H*: 4.75 (9.5), OC*H*$_3$: 3.63 (s); [c]at 70 °C, OC*H*$_3$: 3.77 (s), NC*H*$_2$: 4.09 (2.2), C≡C*H*: 2.18 (2.2 + 2.2); [d]+DMSO, 100 °C, N*H*: 7.04 (4.8+4.7), C*H*O: 8.0 (4.8); [e]at 70 °C, N*H*: 1.64 (br s), N*Me*: 2.48 (s); [f]NC*H*$_2$: 3.72 (17.0+2.3) + 3.51 (17.0+2.2), C≡C*H*: 2.20 (2.2 + 2.3), N*Me*: 2.48 (s); [g]NC*H*$_2$: 3.64 + 3.58 ($J_{gem}$= 17.0), N*Me*: 2.54 (s), COC*H*$_3$: 2.08 (s). | | | | | | | |

**Table V**. $^1$H NMR signals of C4-substituted Uhle's ketones as diethyl ketals ($CDCl_3$, δ, ppm, *J* in Hz)

| | **28**[a] | **29**[b] | **30**[c] | **31**[d] | **32**[e] | **34**[f] |
|---|---|---|---|---|---|---|
| H-2 | 7.25 (2.0) | 7.24 (2.0) | 7.23 (1.8+1.0) | 7.19 (1.9) | 7.15 (1.6+1.1) | 7.22 (1.8+0.9) |
| H-$3_A$ | 3.05 (16.2+3.7) | 2.85 (16.0+3.5) | 3.03 (16.0+4.4+1.0) | 2.96 (16.0+3.2) | 3.10 (16.2+4.8+1.6) | 2.99 (16.0+4.8+0.9) |
| H-$3_B$ | 3.27 (16.2+3.8+2.0) | 3.25 (16.0+4.0+2.0) | 3.21 (16.0+3.9+1.8) | 3.04 (16.0+3.4+1.9) | 3.20 (16.2+5.7+1.1) | 3.16 (16.0+3.9+1.8) |
| H-4 | 4.18 (3.8+3.7) | 3.58 (4.0+3.5) | 4.80 (8.9+4.4+3.9) | 3.27 (3.4+3.2) | 3.57 (5.7+4.8) | 4.72 (8.0+4.8+3.9) |
| H-6 | 7.44(7.4+0.6) | 7.44(7.5+0.7) | 7.42(7.5+0.7) | 7.39(7.3+0.6) | 7.39(7.5+0.6) | 7.42(7.4+0.7) |
| H-7 | 7.31(8.2+7.4) | 7.32(8.2+7.5) | 7.32(8.2+7.5) | 7.27(8.2+7.3) | 7.27(8.3+7.5) | 7.32(8.2+7.4) |
| H-8 | 7.84(8.2+0.6) | 7.85(8.2+0.7) | 7.88(8.2+0.7) | 7.79(8.2+0.6) | 7.82(8.3+0.6) | 7.88(8.2+0.7) |
| Ts-Me | 2.31(s) | 2.34(s) | 2.34(s) | 2.36(s) | 2.31(s) | 2.33(s) |
| Ts-*o*-CH | 7.69(m) | 7.74(m) | 7.74(m) | 7.72(m) | 7.69(m) | 7.74(m) |
| Ts-*m*-CH | 7.17(m) | 7.19(m) | 7.22(m) | 7.17(m) | 7.16(m) | 7.21(m) |
| OC*H*$_2$CH$_3$ | 3.08(m) +3.52(m) 3.67(7.0) | 3.06(m) +3.5(m) 3.7(7.0) | 3.07(m) +3.61(m) 3.45(m)+3.69(m) | 2.98(m) +3.72(m) 3.46(m)+3.63(m) | 3.18(m) +3.42(m) 3.40(m) | 3.06(m)+3.59(m) 3.42(m)+3.67(m) |
| OCH$_2$C*H*$_3$ | 0.92(7.0) 1.3(7.1) | 0.95(7.0) 1.29(7.1) | 0.94(7.0) 1.21(7.1) | 0.88(7.0) 1.26(7.1) | 0.98(7.0) 1.18(7.1) | 0.95(7.0) 1.17(7.0) |
| Side chain | [a]at 70 °C; [b]at 70 °C, N*H*$_2$: 1.38(br s); [c]at rt, C*H*O: 7.97(br s); [d]at 70 °C, N*Me*: 2.33(s); [e]at 50 °C, N*Me*: 2.16 (s), NC*H*$_2$: 3.31 (2.3+2.4), C≡C*H*: 2.10 (2.3+2.4); [f]at 70 °C, CO*Me*: 1.78(s). | | | | | |

**Table VI**. $^{13}C$ NMR signals of C4-substituted C5-protected Uhle's ketones ($CDCl_3$, rt, δ, ppm)

| | **10** | **11** | **12**[a] | **13**[b] | **23**[c] | **24**[d] | **25**[e] | **26**[f] | **28** | **29** | **30**[g] | **31**[h] | **32**[i] | **34**[j] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| C-2 | 120.91 | 120.84 | 121.17 | 120.47 | 120.77<br>+121.39 | 120.70 | 119.88 | 119.86 | 121.39 | 121.77 | 121.73 | 121.28 | 119.98 | 121.59 |
| C-2a | 115.00 | 116.55 | 115.61 | 116.94 | 115.18 | 116.47 | 117.94 | 117.94 | 115.28 | 116.03 | 115.94 | 116.96 | 119.27 | 116.23 |
| C-3 | 25.58 | 27.58 | 26.70 | 24.64 | 26.25,26.92 | 24.30 | 22.02 | 22.80 | 25.11 | 26.38 | 25.69 | 22.59 | 20.04 | 25.68 |
| C-4 | 62.85 | 54.12 | 52.68 | 56.70 | 49.12,54.77 | 61.98 | 64.14 | 64.90 | 59.32 | 50.77 | 48.46 | 59.72 | 63.12 | 49.46 |
| C-5 | 107.40 | 107.90 | 106.53 | 107.76 | 106.16<br>+106.27 | 107.95 | 108.44 | 108.79 | 99.31 | 100.69 | 99.25 | 100.29 | 99.98 | 99.06 |
| C-5a | 130.36 | 131.15 | 130.03 | 132.46 | 129.72<br>+130.73 | 131.25 | 132.87 | 133.07 | 131.42 | 128.72 | 129.80 | 129.42 | 130.84 | 129.80 |
| C-6 | 118.02 | 118.49 | 118.72 | 117.80 | 118.38<br>+118.81 | 118.04 | 117.69 | 117.50 | 120.67 | 121.13 | 120.92 | 120.54 | 119.84 | 120.89 |
| C-7 | 125.68 | 125.45 | 125.64 | 125.41 | 125.70 | 125.30 | 125.47 | 125.37 | 124.95 | 124.79 | 124.74 | 124.49 | 124.66 | 124.78 |
| C-8 | 114.16 | 113.84 | 114.17 | 114.02 | 114.17<br>+114.27 | 113.77 | 113.63 | 113.59 | 113.71 | 113.40 | 114.00 | 113.34 | 113.36 | 113.83 |
| C-8a | 133.27 | 133.41 | 133.35 | 133.70 | 133.35 | 133.27 | 133.31 | 133.27 | 133.47 | 133.46 | 133.89 | 133.52 | 133.67 | 133.57 |
| C-8b | 129.50 | 129.54 | 129.38 | 129.35 | 129.10<br>+129.42 | 129.60 | 129.65 | 129.90 | 128.22 | 128.42 | 128.12 | 129.26 | 129.95 | 127.98 |
| Ts-Me | 21.51 | 21.49 | 21.51 | 21.56 | 21.49 | 21.48 | 21.49 | 21.46 | 21.46 | 21.47 | 21.28 | 21.48 | 21.46 | 21.48 |
| Ts-C1' | 135.48 | 135.55 | 135.41 | 135.98 | 135.33 | 135.55 | 135.50 | 135.33 | 135.31 | 135.35 | 135.97 | 135.80 | 135.39 | 135.29 |
| Ts-*o*-CH | 126.77 | 126.77 | 126.76 | 126.73 | 126.75<br>+126.77 | 126.76 | 126.71 | 126.67 | 126.64 | 126.69 | 126.76 | 126.80 | 126.61 | 126.77 |
| Ts-*m*-CH | 129.89 | 129.84 | 129.91 | 129.81 | 129.92<br>+129.94 | 129.80 | 129.78 | 129.77 | 129.73 | 129.73 | 129.71 | 129.71 | 129.60 | 129.77 |
| Ts-*p*-C | 144.93 | 144.80 | 144.95 | 144.75 | 145.02<br>+145.06 | 144.74 | 144.72 | 144.75 | 144.73 | 144.69 | 144.68 | 144.55 | 144.55 | 144.81 |
| $O(CH_2)_2O$ | 65.82<br>+66.55 | 65.04<br>+66.58 | 65.08<br>+66.51 | 63.88<br>+67.13 | 64.85,65.20<br>65.29,67.02 | 65.27<br>+65.87 | 65.09<br>+66.50 | 66.18<br>+66.41 | | | | | | |
| $OCH_2CH_3$ | | | | | | | | | 56.32<br>+57.46 | 55.69<br>+57.52 | 56.58<br>+57.76 | 55.69<br>+56.96 | 56.50<br>+57.37 | 56.52<br>+57.52 |
| $OCH_2CH_3$ | | | | | | | | | 14.73<br>+14.98 | 14.81<br>+15.33 | 14.66<br>+14.97 | 14.84<br>+15.33 | 15.13 | 14.77<br>+15.11 |
| Side chain | [a]OMe: 52.16, $CO_2$: 156.68; [b]at 70 °C, OMe: 52.92, $CO_2$: 157.04, $CH_2$: 33.89, C≡CH: 81.51+70.12; [c]CHO: 160.83+164.49; [d]NMe: 34.67; [e]NMe: 39.27, $NCH_2$: 45.38, C≡CH: 81.14+72.23; [f]NMe: 40.42, $NCH_2$: 64.42, COMe: 209.37+26.93; [g]CHO: 160.26; [h]NMe: 34.51; [i]NMe: 38.49, $NCH_2$: 44.86, C≡CH: 81.18+72.27; [j]Me: 23.36, NCO: 169.58. | | | | | | | | | | | | | |

**1-(Toluene-4-sulfonyl)-3,4-dihydro-1*H*-benzo[*c,d*]indol-5-one** (**7**) To a cold (0 °C, ice-bath) solution of Uhle's ketone (**6**, 10.27 g; 60 mmol) in dry $CH_2Cl_2$ (500 mL) tetrabutylammonium hydrogen sulfate (2.28 g; 6.7 mmol) and powdered potassium hydroxide (17.1 g; 305 mmol) were added. The solution was stirred at 0 °C for 10 min, then 4-toluenesulfonyl chloride (19.0 g; 100 mmol) was added dropwise in a solution of $CH_2Cl_2$ (500 mL) during about 15 min at the above temperature. The reaction mixture was stirred for 1.5 h while the temperature of the mixture was allowed to rt, then poured into a mixture of $CHCl_3$ (1.5 L), saturated aqueous $NaHCO_3$ solution (0.5 L) and water (0.5 L). After shaking the organic phase separated, washed with water (2x1 L), dried ($Na_2SO_4$). The filtrate was evaporated under reduced pressure to yield an oil which on trituration with hexane (200 mL) afforded pale yellow crystals. The crystals were filtered off, washed with ether (2x50 mL) to yield **7** (17.71 g; 90.7 %), mp 157-159 °C [lit.,[3b] mp 143-144 and 157-158 °C ]. IR (KBr): 1674, 1604, 1376, 1360, 1303, 1178 $cm^{-1}$. MS (*m*/*z*, %): 325 (100, $M^+$), 170 (87), 155 (40), 142 (13), 155 (63), 91 (93). Anal. Calcd for $C_{18}H_{15}NO_3S$; C, 66.44, H, 4.65, N, 4.30, S, 9.85. Found C, 66.39, H, 4.67, N, 4.28, S, 9.88.

**4-Bromo-1-(toluene-4-sulfonyl)-3,4-dihydro-1*H*-benzo[*c,d*]indol-5-one** (**8**) To a cold solution (0 °C) of **7** (17.08 g; 52.5 mmol) in a mixture of $CCl_4$ (260 mL), $CHCl_3$ (100 mL) and ether (100 mL) bromine-dioxane complex (16.3 g; 65.7 mmol) in a mixture of $CCl_4$ (150 mL), $CHCl_3$ (50 mL) and ether (100 mL) was added dropwise during about 3 h while the temperature was kept at 5-10 °C. The mixture was treated with aqueous $Na_2S_2O_3$ solution (10 %, 500 mL) and diluted with $CHCl_3$ (1 L). After extraction the phases were separated and the aqueous phase was extracted with $CHCl_3$ (2x0.5 L). The combined organic phase was washed with water (2x0.5 L), dried ($Na_2SO_4$) and evaporated under reduced pressure. The residue was treated with a mixture of diisopropyl ether + acetonitrile (100 mL + 10 mL) to yield **8** as crystals (16.0 g; 77.0 %), mp 159-161 °C [lit.,[3b] mp 163-164 °C ]. IR (KBr): 1691, 1606, 1442, 1381, 1364, 1179 $cm^{-1}$. MS (*m*/*z*, %): 405 (39. M+H), 404 (37, $M^+$), 323 (10), 169 (22), 155 (52), 140 (14), 91 (100). Anal. Calcd for $C_{18}H_{14}NO_3BrS$: C, 53.48, H, 3.49, N, 3.46, Br, 19.76, S, 7.93. Found: C, 53.31, H, 3.45, N, 3.29, Br, 19.85, S, 8.01.

**4-Azido-1-(toluene-4-sulfonyl)-3,4-dihydro-1*H*-benzo[*c,d*]indol-5-one** (**9**) Bromo ketone (**8**) (37.0 g; 91.5 mmol) was converted into azido ketone (**9**) (29.6 g; 88 %) as described in ref. 3c, mp 169-174 °C [lit.,[3c] mp 176-178 °C ]. IR (KBr): 2117, 1684, 1607, 1380, 1179 $cm^{-1}$; MS (*m*/*z*, %): 366 (13, $M^+$), 338 (100), 325 (13), 283 (10), 218 (6). Anal. Calcd for $C_{18}H_{14}N_4O_3S$: C, 59.01, H, 3.85, N, 15.29, S, 8.75. Found: C, 59.12, H, 3.86, N, 15.28, S, 8.69.

**4-Azido-5,5-ethylenedioxy-1-(toluene-4-sulfonyl)-3,4-dihydro-1*H*-benzo[*c,d*]indol** (**10**) Protection of the carbonyl function of **9** (15 g; 40.9 mmol) was accomplished similarly to Bowman's method.[3d] The

obtained crude product (**10**, red oil, 15.9 g; 95 %) could be used without further purification in the next step. An analytical sample was purified by column chromatography (eluent: $CHCl_3$ – hexane, 8/2) to yield a colorless oil. IR (KBr): 3240, 3200, 2900, 2250, 1600, 1450 $cm^{-1}$. Anal. Calcd for $C_{20}H_{18}N_4O_4S$: C, 58.53, H, 4.42, N, 13.65, S, 7.81. Found: C, 58.47, H, 4.47, N, 13.59, S, 7.88.

**4-Amino-5,5-ethylenedioxy-1-(toluene-4-sulfonyl)-3,4-dihydro-1*H*-benzo[*c,d*]indole** (**11**)[3d] To a cold solution (0 $^oC$) of **10** (13.4 g; 32.6 mmol) in dry THF (1 L), LAH (12.0 g; 0.31 mol) was added in portion wise during about 0.5 h. The reaction mixture was stirred at the above temperature for 0.5 h, then the temperature was allowed to warm up to rt. After 2 h the mixture was cooled again with an ice-bath and water (200 mL) was added in dropwise under stirring. The resulting precipitate was filtered off, washed with $CHCl_3$ (0.5 L) and the combined filtrates were evaporated under reduced pressure. The residue was dissolved in a mixture of $CHCl_3$ (1.2 L) and water (0.5 L). After extraction, the phases were separated and the organic phase was washed with water (2x0.3 L), dried ($Na_2SO_4$). The filtrate was evaporated to yield **11** (11.8 g; 97 %) as a pure oil. IR (KBr): 3390, 2830, 1580 $cm^{-1}$. Anal. Calcd for $C_{20}H_{20}N_2O_4S$: C, 62.48, H, 5.24, N, 7.29, S, 8.34. Found: C, 62.40, H, 5.21, N, 7.28, S, 8.35.

**4-(*N*-Methoxycarbonyl)amino-5,5-ethylenedioxy-1-(toluene-4-sulfonyl)-3,4-dihydro-1*H*-benzo[*c,d*]-indole** (**12**)[3d] To a cold (0 $^oC$) solution of **11** (2.88 g; 7.5 mmol) in a mixture of THF (200 mL) and aqueous saturated $NaHCO_3$ solution (50 mL) methyl chloroformate (1.0 mL; 12.0 mmol) was added in THF (5 mL) and stirred for 0.5 h. The reaction mixture was diluted with a mixture of $CHCl_3$ (300 mL) and cold water (100 mL). The phases were separated and the organic layer was washed with water (2x200 mL), dried ($Na_2SO_4$). The filtrate was evaporated under reduced pressure and the residue (2.9 g) was purified by column chromatography (Merck 9385, eluent: $CHCl_3$ – hexane, 3/2, then $CHCl_3$) to yield **12** (2.38 g; 71.9 %) as a colorless oil. IR (KBr): 3350, 1726, 1522, 1362, 1173 $cm^{-1}$. MS (*m*/z, %): 442 (53, $M^+$), 397 (100), 381 (40), 368 (30), 308 (39), 259 (9), 211 (57), 200 (50), 184 (31). Anal. Calcd for $C_{22}H_{22}N_2O_6S$: C, 59.72, H, 5.01, N, 6.33, S, 7.25. Found: C, 59.68, H, 4.99, N, 6.35, S, 7-28.

**4-[*N*-(Methoxycarbonyl)-*N*-propargyl]amino-5,5-ethylenedioxy-1-(toluene-4-sulfonyl)-3,4-dihydro-1*H*-benzo[*c,d*]indole** (**13**) To a solution of **12** (4.4 g; 10.0 mmol) in a mixture of benzene (30 mL) and DMF (60 mL) sodium hydride (50 % oil dispersion; 2.0 g; 41.6 mmol, washed with hexane) was added in a suspension of benzene (5 mL) at rt, and the mixture was stirred for 1 h. To the mixture propargyl bromide (4.0 mL, 35.6 mmol, 80 % solution in toluene; Aldrich P5,100-1) was added and the reaction mixture was stirred further for 3 h, then poured into a mixture of ethyl acetate (1.0 L), crushed ice (500 g) and aqueous HCl solution (1 N, 80 mL). The phases were separated and the organic layer was washed with cold water (2x250 mL), dried ($Na_2SO_4$). The filtrate was evaporated under reduced pressure and the

residue (5.3 g) was chromatographed (Merck 9385, eluent: $CHCl_3$ – acetone, 500/25) to yield **13** (3.7 g; 77 %) as a colorless oil which was crystallized from ether (10 mLl) to yield **13** (3.2 g; 68 %), mp 150-151 °C [lit.,[3d] mp 153-157 °C ]. IR (KBr): 3250, 1695 $cm^{-1}$. MS (*m*/*z*, %): 480 (34, $M^+$), 440 (63), 434 (69), 368 (36), 325 (100), 308 (23), 349 (51), 200 (52), 156 (39). Anal. Calcd for $C_{25}H_{24}N_2O_6S$: C, 62.49, H, 5.03, N, 5.83, S, 6.67. Found: C, 62.51, H, 4.98, N, 5.81, S, 6.71.

**4-[*N*-(Methoxycarbonyl)-*N*-acetonyl]amino-1-(toluene-4-sulfonyl)-3,4-dihydro-1*H*-benzo[*c*,*d*]indol-5-one** (**14**) To a solution of **13** (1.8 g; 3.75 mmol) in a mixture of dioxane (70 mL) and $H_2SO_4$ solution (2.5 N, 18 mL) $HgSO_4$ (160 mg; 0.54 mmol) was added and the mixture was stirred at 90 °C for 1 h. The mixture was cooled to rt, then diluted with $CHCl_3$ (600 mL) and cold water (250 mL). The phases were separated and the aqueous layer was washed with $CHCl_3$ (250 mL). The combined organic phases were washed with cold water (250 mL), dried ($Na_2SO_4$). The filtrate was evaporated under reduced pressure and the residue (2.2 g) was chromatographed (Merck 9385, eluent: $CHCl_3$ – hexane - ethyl acetate, 400/75/25) to yield **14** (1.68 g; 98.8 %) as a semisolid material, mp 98-101 °C (from a mixture of diisopropyl ether and hexane, 1/1) [lit.,[3d] mp 159-161 °C ]. IR (KBr): 2880, 1730, 1708, 1607, 1461, 1360, 1178 $cm^{-1}$. MS (*m*/*z*, %): 454 (12, $M^+$), 396 (8), 323 (100), 299 (7), 267 (8), 223 (7), 184 (7), 169 (15), 155 (48). Anal. Calcd for $C_{23}H_{22}N_2O_6S$: C, 60.78, H, 4.88, N, 6.16, S, 7.05. Found: C, 60.75, H, 4.87, N, 6.21, S, 7.11.

**4-(*N*-Methoxycarbonyl)amino-1-(toluene-4-sulfonyl)-1*H*-benzo[*c*,*d*]indol-5-one** (**15**) To a solution of **14** (147 mg; 0.323 mmol) in THF (5 mL) at rt LiBr (171 mg; 1.97 mmol) in THF (5 mL) and TEA (171 mg; 1.693 mmol) in THF (2 mL) were added. The mixture was stirred for 3 d at rt, then evaporated under reduced pressure. The residue was chromatographed (Merck 9385, eluent: hexane - ethyl acetate, 1/1) to yield **15** (15 mg; 11.7 %) as a pure oil. IR (KBr): 3369, 2956, 2853, 1723, 1641, 1606, 1512, 1132 $cm^{-1}$. MS (FAB): 396.0779 (calcd 396.0780, $C_{20}H_{16}N_2O_5S$). $^1$H NMR (400 MHz, $CDCl_3$), δ: 2.35 (3H, s, Ts-Me), 3.81 (3H, s, OMe), 7.26 (2H, m, Ts-*m*-CH), 7.61 (1H, t, *J*= 7.9 Hz, H-7), 7.82 (2H, m, Ts-*o*-CH), 7.87 (1H, s, H-2), 8.01 (1H, s, NHCO), 8.12 (1H, dd, *J*= 7.9 + 1.2 Hz, H-6), 8.22 (1H, dd, *J*= 7.9 + 1.2 Hz, H-8), 8.30 (1H, s, H-3). $^{13}$C NMR (100 MHz, $CDCl_3$), δ: 21.75 (Ts-Me), 52.63 (OMe), 111.29 (C-3), 115.64 (C-2a), 123.54 (C-6), 124.85 (C-5a), 127.09 (C-7), 127.14 (Ts-*o*-CH), 128.56 (C-8b), 130.40 (Ts-*m*-CH), 134.12 (C-8a), 135.40 (Ts-C1'), 145.92 (Ts-*p*-C), 154.15 (COO), 178.05 (C-5).

**4-(Toluene-4-sulfonyl)-4,5,8,9-tetrahydro-7-methoxycarbonyl-9-ethoxy-9-methyl-7*H*-indolo[3,4-*gh*]-[1,4]benzoxazine** (**16**) To a solution of **14** (150 mg; 0.33 mmol) in benzene (20 mL) 4-toluenesulfonic acid monohydrate (180 mg; 0.94 mmol) was added, and the mixture was refluxed for 2 h. The reaction mixture was evaporated under reduced pressure and the residue was purified by chromatography (Merck

9385, eluent: $CHCl_3$ – hexane, 7/3) to yield **16** (65 mg; 41.2 %) as a pure oil, mp 151-153 °C (from MeOH). IR (KBr): 2950, 1711, 1493, 1473, 1448, 1358, 1166cm$^{-1}$. MS (*m*/*z*, %): 482.1519 (calcd 482.1512, $C_{25}H_{26}N_2O_6S$, 100, $M^+$). $^1$H NMR (400 MHz, $CDCl_3$), δ: 1.02 (3H, t, *J*= 6.8 Hz, $CH_2CH_3$), 1.63 (3H, s, C9-Me), 2.34 (3H, s, Ts-Me), 3.16 (1H, d, $J_{gem}$= 13.1 Hz, H-8$_A$), 3.63 (2H, m, $OCH_2CH_3$), 3.81 (3H, s, OMe), 4.33 (1H, d, $J_{gem}$= 13.1 Hz, H-8$_B$), 5.06 (2H, s, H-5), 7.18 (2H, m, Ts-*m*-CH), 7.34 (1H, dd, *J*= 8.2 + 7.4 Hz, H-2), 7.41 (1H, dd, *J*= 7.04 + 0.8 Hz, H-1), 7.44 (1H, dd, *J*= 8.2 + 0.8 Hz, H-3), 7.48 (1H, s, H-6), 7.76 (2H, m, Ts-*o*-CH). $^{13}$C NMR (100 MHz, $CDCl_3$), δ: 15.53 ($CH_2CH_3$), 21.0 (Ts-Me), 21.43 (C9-Me), 50.18 (C-8), 53.46 (OMe), 55.95 (C-5), 57.48 ($OCH_2CH_3$), 97.85 (C-9), 106.96 (C-1), 113.67 (C-3), 114.85 (C-6a), 114.94 (C-6), 123.19 (C-10b), 126.12 (C-10a), 127.33 (Ts-*o*-CH), 128.31 (C-3b), 128.75 (C-2), 130.02 (Ts-*m*-CH), 134.66 (Ts-C1'), 138.16 (C-5a), 142.77 (C-3a), 144.48 (Ts-*p*-C), 155.82 (NCOO). [The presence and position of the ethoxy and methyl groups at C-9 follow from the long-range heterocorrelation of the protons with C-9 and C-8 carbons].

**4-(Toluene-4-sulfonyl)-7-methoxycarbonyl-4,5,8,10-tetrahydro-7*H*-indolo[4,3-*fg*]quinolin-9-one** (**17**) To a solution of **14** (100 mg; 0.22 mmol) in benzene (15 mL) KF/$Al_2O_3$ (2.0 g; 3.6 mmol, $Al_2O_3$: Aldrich – 19,944-3) was added, and the mixture was refluxed for 2 h. Upon cooling, the mixture was filtered, the filtrate washed with benzene (4x10 mL) and $CHCl_3$ (5x10 mL). The filtrates were evaporated under reduced pressure to yield **17** (60 mg; 62.5 %) as a pure oil. IR (KBr): 2990, 2970, 1736, 1708, 1625, 1445, 13601180 cm$^{-1}$. MS (*m*/*z*, %): 436.1086 (calcd 436.1096, $C_{23}H_{20}N_2O_5S$, 38, $M^+$), 323 (100), 281 (19), 253 (11), 225 (10), 193 (13), 169 (14), 155 (51). $^1$H NMR (400 MHz, $CDCl_3$), δ: 2.34 (3H, s, Ts-Me), 3.78 (2H, s, H-10), 3.82 (3H, s, OMe), 4.30 (2H, s, H-8), 5.18 (2H, s, H-5), 7.27 (2H, m, Ts-*m*-CH), 7.29 (1H, dd, *J*= 7.0 + 1.9 Hz, H-1),7.46-7.52 (2H, m, H-2 + H-3), 7.50 (1H, s, H-6), 7.78 (2H, m, Ts-*o*-CH). $^{13}$C NMR (100 MHz, $CDCl_3$), δ: 21.69 (Ts-Me), 39.42 (C-10), 53.59 (C-8), 53.80 (OMe), 55.88 (C-5), 107.39 (C-1), 114.69 (C-3), 115.37 (C-6), 126.98 (C-10b), 127.31(Ts-*o*-CH), 128.51 (C-3b), 129.91 (C-6a), 130.12 (Ts-*m*-CH), 130.47 (C-2), 134.47 (C-10a), 134.58 (Ts-C1'), 137.88 (C-5a), 143.60 (C-3a), 144.76 (Ts-*p*-C), 154.76 (NCOO), 205.87 (C-9).

**(+)-1-(Toluene-4-sulfonyl)-8-oxoergolene** (**20**) To a cold (0 °C) solution of **18** (238 mg; 1.0 mmol) in dry $CH_2Cl_2$ (20 mL) tetrabutylammonium hydrogen sulfate (40 mg; 0.12 mmol) and powdered KOH (280 mg; 5.0 mmol) were added. The solution was stirred at 0 °C for 5 min, then 4-toluenesulfonyl chloride (316 mg; 1.66 mmol) was added dropwise in a solution of $CH_2Cl_2$ (10 mL) during about 1-2 min at the above temperature. The reaction mixture was stirred for 2 h while the temperature was allowed to warm to rt, then poured into a mixture of cold $CHCl_3$ (50 mL) and ice-water (50 mL). After shaking the organic phase was separated, washed with cold water (2x30 mL), dried ($Na_2SO_4$) and evaporated under reduced pressure. The obtained oil was treated with *n*-hexane (10 mL) and the precipitated crystals were filtered

off, washed with a mixture of ether and hexane (1/1, 2x10 mL) then with a mixture of hexane – ethyl acetate (2/1, 10 mL) to yield **20** (260 mg; 66.0 %) as a white solid, mp ≈ 300 °C (decomp). $[\alpha]_D$ = + 138 °C (c= 0.5, $CHCl_3$). IR (KBr): 3112, 2961, 2764, 1674, 1620, 1597, 1364, 1124 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$), δ: 2.35 (3H, s, Ts-Me), 2.55 (3H, s, N-Me), 2.74 (1H, m, *J*= 15.3 + 11.5 + 2.0 Hz, H-$4_A$), 3.39 (1H, d, *J*= 16.0 Hz), 3.39 (1H, m, H-5), 3.44 (1H, d, *J*= 16.0 Hz, H-$7_A$), 3.52 (1H, d, J= 16.0 Hz, H-$7_B$), 3.53 (1H, dd, *J*= 15.3 + 6.3 Hz, H-$4_B$), 6.73 (1H, d, *J*= 2.1 Hz, H-9), 7.24 (2H, m, Ts-*m*-CH), 7.33 (1H, d, *J*= 2.0 Hz, H-2), 7.38 (1H, dd, *J*= 8.1 + 7.6 Hz, H-13), 7.47 (1H, dd, *J*= 7.6 + 0.5 Hz, H-12), 7.78 (2H, m, Ts-*o*-CH), 7.94 (1H, dd, *J*= 8.1 + 0.5 Hz, H-14). $^{13}C$ NMR (100 MHz, $CDCl_3$), δ: 21.55 (Ts-Me), 25.83 (C-4), 42.16 (N-Me), 61.23 (C-5), 63.21 (C-7), 115.69 (C-12), 116.27 (C-3), 118.68 (C-14), 120.78 (C-9), 121.31 (C-2), 125.87 (C-16), 126.10 (C-13), 126.73 (Ts-*o*-CH), 129.71 (C-11), 129.94 (Ts-*m*-CH), 133.40 (C-15), 135.22 (Ts-C1'), 145.10 (Ts-*p*-C), 154.03 (C-10), 195.07 (C-8). Anal. Calcd for $C_{22}H_{20}N_2O_3S$: C, 67.33, H, 5.14, N, 7.14, S, 8.17. Found: C, 67.38, H, 5.21, N, 7.22, S, 8.15.

**Equilibration experiment of 21 with 22**. A solution of **20** (50 mg; 0.127 mmol) in DMSO-$d_6$ (0.6 mL) was placed in an NMR tube and $CF_3CO_2D$ (3 drops) was added. The sealed tube, in argon atmosphere, was kept at rt for 5 min. At this point, $^1H$ and $^{13}C$ NMR spectra showed the presence of **21**. $^1H$ NMR (400 MHz, DMSO-$d_6$ + $CF_3CO_2D$) δ: 2.33 (3H, s, Ts-Me), 3.06 (1H, m, *J*= 15.4 + 11.9 + 2.0 Hz, H-$4_A$), 3.14 (3H, s, N-Me), 3.86 (1H, dd, *J*= 15.4 + 6.5 Hz, H-$4_B$), 4.18 (1H, d, *J*= 16.0 Hz, H-$7_A$), 4.26 (1H, d, J= 16.0 Hz, H-$7_B$), 4.86 (1H, m, *J*= 11.9 + 6.5 + 2.0 Hz, H-5), 7.15 (1H, d, *J*= 2.0 Hz, H-9), 7.41 (2H, m, Ts-*m*-CH), 7.52 (1H, dd, *J*= 8.0 + 7.8 Hz, H-13), 7.81 (1H, d, *J*= 2.0 Hz, H-2), 7.90 (1H, d, *J*= 7.8 Hz, H-12), 7.93 (2H, m, Ts-*o*-CH), 8.04 (1H, d, *J*= 8.1 Hz, H-14) 11.25 (1H, br s, $NH^+$). $^{13}C$ NMR (100 MHz), δ: 20.97 (Ts-Me), 22.60 (C-4), 40.15 (N-Me), 58.94 (C-7), 59.35 (C-5), 113.96 (C-3), 116.35 (C-12), 119.98 (C-14), 120.70 (C-9), 122.87 (C-2), 123.90 (C-16), 126.57 (C-13), 126.74 (Ts-*o*-CH), 128.83 (C-11), 130.34 (Ts-*m*-CH), 132.63 (C-15), 134.17 (Ts-C1'), 145.75 (Ts-*p*-C), 148.77 (C-10), 188.52 (C-8).

The final stage, checked after about 5 weeks, indicated the dominant form of **22** (**22**:**21** ≈ 9:1). $^1H$ NMR of **22** (400 MHz) δ: 2.28 (3H, s, Ts-Me), 4.57 (3H, s, N-Me), 5.38 (2H, s, H-5), 7.35 (2H, m, Ts-*m*-CH), 7.68 (1H, d, *J*= 7.8 Hz, H-3), 7.82 (1H, dd, J= 8.0 + 7.8 Hz, H-2), 7.84 (2H, m, Ts-*o*-CH), 8.00 (1H, s, H-6), 8.18 (1H, d, *J*= 8.0 Hz, H-1), 9.12 (1H, s, H-8), 9.13 (1H, s, H-10). $^{13}C$ NMR (100 MHz), δ: 21.53 (Ts-Me), 47.12 (N-Me), 56.61 (C-5), 108.20 (C-6), 112.15 (C-3), 114.97 (C-10a), 117.42 (C-1), 125.09 (C-10), 126.79 (C-3b), 127.31 (C-10b), 127.61(Ts-*o*-CH), 130.83 (Ts-*m*-CH), 132.97 (C-2), 133.69 (C-5a), 136.37 (Ts-C1'), 139.56 (C-8), 141.34 (C-6a), 143.45 (C-3a), 145.71 (Ts-*p*-C), 152.97 (C-9). [The aromatisation of ring-D follows from the steric correlations of protons H-8 and H-10 with other groups. Thus NOE measurements revealed the steric proximity between H-1 and H-10 and that of *N*-Me and H-8].

**4-*N*-(Formyl)amino-5,5-ethylenedioxy-1-(toluene-4-sulfonyl)-3,4-dihydro-1*H*-benzo[*c,d*]indole** (**23**)

*Method a):* To a solution of **11** (8.9 g; 23.2 mmol) in a mixture of diisopropyl ether (100 mL) and methyl-*tert*-butyl ether (50 mL) ethyl formate (35.0 mL; 642 mmol) was added and the reaction mixture was refluxed for 30 h. Upon cooling, the solvents were evaporated under reduced pressure and the residue was crystallized from a mixture of diisopropyl ether (35 mL), methyl-*tert*-butyl ether (15 mL) and acetonitrile (10 mL) to yield **23** (6.4 g; 67.0 %) as crystals, mp 152-153 $^{o}$C. IR (KBr): 3300, 2950, 2920, 2850, 1680, 1660, 1580, 1520, 1430, 1350, 1150, 1020 cm$^{-1}$. Anal. Calcd for $C_{21}H_{20}N_2O_5S$: C, 61.15, H, 4.89, N, 6.79, S, 7.77. Found: C, 61.23, H, 4.87, N, 6.73, S, 7.75.

*Method b):*The mixed anhydride was prepared from acetic anhydride (0.24 mL; 2.5 mmol) and formic acid (0.09 mL; 2.5 mmol) in $CH_2Cl_2$ (5.0 mL) at 50 $^{o}$C. After being stirred for 1 h, the mixture was cooled to rt and a solution of **11** (768 mg; 2.0 mmol) in a mixture of $CH_2Cl_2$ (8 mL) and pyridine (0.5 mL) was added. The reaction mixture was stirred at 50 $^{o}$C for 1.5 h and cooled again to rt and poured into a mixture of ice-water (20 mL), $CHCl_3$ (100 mL) and aqueous concentrated ammonium hydroxide solution (2.0 mL). The organic phase was separated, washed with cold water (3x20mL), dried ($Na_2SO_4$). The filtrate was evaporated under reduced pressure and the residue was crystallized from a mixture of ether and diisopropyl ether (5 + 5 mL) to yield **23** (694 g; 84.2 %).

**4-*N*-(Methyl)amino-5,5-ethylenedioxy-1-(toluene-4-sulfonyl)-3,4-dihydro-1*H*-benzo[*c,d*]indole** (**24**)

To a solution of **23** (6.0 g; 14.5 mmol) in THF (100 mL) LAH (2.4 g; 63.1 mmol) was added in a suspension of THF (50 mL) at 55-60 $^{o}$C during about 15 min. The reaction mixture was stirred at the above temperature for 3 h, then was cooled with an ice-bath and poured into a mixture of $CHCl_3$ (700 mL), crushed-ice (500 g) and aqueous concentrated ammonium hydroxide solution (40 mL). The precipitate was filtered off, washed with $CHCl_3$ (3x100 mL). The combined organic phases were washed with water (2x0.5 L), dried ($Na_2SO_4$). The filtrate was evaporated under reduced pressure and the residue (5.9 g) was purified by column chromatography (Merck 9385, eluent: $CHCl_3$ – hexane - MeOH, 5/1/0.1) to yield **24** (3.7 g; 63.9 %) as a pure oil. IR (KBr): 3250, 2850, 1600, 1439, 1360, 1176, 1037 cm$^{-1}$. Anal. Calcd for $C_{21}H_{22}N_2O_4S$: C, 63.30, H, 5.56, N, 7.03, S, 8.05. Found: C, 63.28, H, 5.49, N, 7.00, S, 8.02.

**4-[*N*-(Methyl)-*N*-propargyl]amino-5,5-ethylenedioxy-1-(toluene-4-sulfonyl)-3,4-dihydro-1*H*-benzo-[*c,d*]indole** (**25**) To a solution of **24** (3.7 g; 9.3 mmol) in acetone (200 mL) dry $K_2CO_3$ (4.0 g; 29.0 mmol) and propargyl bromide (4.0 mL; 35.6 mmol) were added and the reaction mixture was stirred at 80 $^{o}$C for 12 h. The solvent was evaporated under reduced pressure and the residue was dissolved in a mixture of $CHCl_3$ (400 mL) and water (100 mL). The organic phase was washed with water (3x100 mL), dried ($Na_2SO_4$). The filtrate was evaporated under reduced pressure and the residue (3.8 g) was purified by column chromatography (Merck 9385, eluent: $CHCl_3$ – hexane, 8/2) to yield **25** (2.7 g; 66 %) as a pure

oil. IR (KBr): 3290, 2888, 1600, 1439, 1375, 1360, 1172 $cm^{-1}$. MS (*m*/*z*, %): 436 (48, $M^+$), 369 (9), 311 (11), 281 (92), 253 (23), 237 (12), 209 (100), 170 (24), 156 (32). Anal. Calcd for $C_{24}H_{24}N_2O_4S$: C, 66.04, H, 5.54, N, 6.42, S, 7.34. Found: C, 66.01, H, 5.50, N, 6.39, S, 7.35.

**4-[*N*-(Methyl)-*N*-acetonyl]amino-5,5-ethylenedioxy-1-(toluene-4-sulfonyl)-3,4-dihydro-1*H*-benzo-[*c*,*d*]indole** (**26**) To a solution of **25** (2.8 g; 6.42 mmol) in MeOH (300 mL) at rt a Hg-salt catalyst was added during about 2-3 h and the reaction mixture was stirred overnight. [The catalyst was prepared in the following way: to a suspension of mercury(II)oxide /red/ (1.0 g; 4.6 mmol) in MeOH (2 mL) boron trifluoride diethyl etherate (0.4 mL; 3.15 mmol) and TFA (1.0 mL; 13.0 mmol) were added. The mixture was stirred at rt for 0.5 h]. The reaction mixture was evaporated under reduced pressure and the residue was treated with NaOH solution (0.5 N, 100 mL). The precipitated crystals were filtered off, washed with water (3x20 mL) and MeOH (2x5 mL) to yield a crude product (3.0 g) which was purified by column chromatography (Merck 9385, eluent: $CHCl_3$ – acetone - MeOH, 15/5/0.5) to yield **26** (1.62 g; 56 %) as a pure oil, mp 96-97 $^oC$ (from ether). IR (KBr): 2922, 1722, 1600, 1440, 1359, 1172 $cm^{-1}$. MS (CI, *m*/*z*, %): 454.1553 (calcd 454.1562, $C_{24}H_{26}N_2O_5S$, 14, $M^+$), 411 (100), 398 (19), 367 (5), 339 (90), 329 (21), 299 (34), 243 (37), 227 (53), 200 (38), 156 (38), 91 (83).

**4-(Toluene-4-sulfonyl)-4,5,8,9,11,12-hexahydro-7,9-dimethyl-7*H*-indolo[3,4-*gh*][1,7]benzo-(7-aza-10,13-dioxa)cyclononan-9-ol** (**27**) To a solution of **26** (180 mg; 0.396 mmol) in dry $CHCl_3$ (20 mL) trimethylsilyl iodide (240 mg; 1.2 mmol) in $CHCl_3$ (2 mL) was added at rt and the mixture was stirred for 6 h. The reaction mixture was poured into a mixture of $CHCl_3$ (100 mL), saturated $NaHCO_3$ solution (20 mL) and aqueous $Na_2S_2O_3$ solution (10 %, 20 mL). The organic phase was separated, washed with water (2x20 mL), dried ($Na_2SO_4$). The filtrate was evaporated under reduced pressure and the residue (225 mg) was purified by column chromatography (Merck 9385, eluent: $CHCl_3$ – hexane, 1/1; $CHCl_3$; $CHCl_3$ – acetone, 20/1) to yield **27** (44 mg; 24.1 %) as a pure oil. IR (KBr): 3417, 2924, 1629, 1604, 1384, 1354, 1163 $cm^{-1}$. MS (*m*/*z*, %): 454.1554 (calcd 454.1562, $C_{24}H_{26}N_2O_5S$, 100, $M^+$), 422 (2), 409 (5), 392 (8), 365 (18), 353 (13), 324 (3), 298 (3), 253 (5), 237 (13), 211 (35), 197 (38). $^1H$ NMR (400 MHz, $CDCl_3$), δ: 1.60 (3H, s, C9-Me), 1.8 (1H, br s, OH), 2.32 (3H, s, Ts-Me), 2.99 (3H, s, N-Me), 3.12 (1H, d, *J*= 11.7 Hz, H-$8_A$), 3.29 (1H, d, *J*= 11.7 Hz, H-$8_B$), 3.44-3.76 (4H, m, H-11 + H-12), 5.06 (2H, s, H-5), 6.68 (1H, s, H-6), 7.19 (2H, m, Ts-*m*-CH), 7.20 (1H, dd, *J*= 8.0 + 1.5 Hz, H-3), 7.29 (1H, t, *J*= 8.0 Hz, H-2), 7.33 (1H, dd, J= 8.0 + 1.5 Hz, H-1), 7.77 (2H, m, Ts-*o*-CH). $^{13}C$ NMR (100 MHz, $CDCl_3$), δ: 21.65 (Ts-Me), 22.10 (C9-Me), 40.15 (N-Me), 56.19 (C-5), 57.52 (C-8), 62.00 + 63.30 (C-11 + C-12), 96.46 (C-9), 104.18 (C-6), 106.08 (C-1), 112.24 (C-3), 123.18 (C-13b), 124.80 (C-3b), 127.34 (Ts-*o*-CH), 128.04 (C-6a), 129.03 (C-2), 129.97 (Ts-*m*-CH), 132.67 (C-13a), 133.59 (C-5a), 134.88 (Ts-C1), 142.97 (C-3a), 144.31 (Ts-*p*-C).

**4-Azido-5,5-diethoxy-1-(toluene-4-sulfonyl)-3,4-dihydro-1*H*-benzo[*c,d*]indole** (**28**) To a solution of **9** (12.62 g; 34.5 mmol) in a mixture of dry $CHCl_3$ (860 mL), dry EtOH (70.0 mL; 1.2 mol) and triethyl orthoformate (35.0 mL; 210 mmol), boron trifluoride diethyl etherate (40.0 mL; 315 mmol) and molecular sieves-4 Å (10.0 g) were added at rt and the reaction mixture was stirred at rt for 24 h. The mixture was filtered and the filtrate was cooled to 0-5 $^oC$. The solution was poured into a mixture of cold $CHCl_3$ (2.0 L) and cold saturated aqueous $NaHCO_3$ solution (1.0 L). The phases were separated and the organic phase was washed with cold saturated aqueous $NaHCO_3$ solution (2x0.5 L) and cold water (2x0.5 L), dried ($Na_2SO_4$). The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography (Merck 9385, eluent: $CHCl_3$ – hexane, 1/1; $CHCl_3$ – hexane, 8/2) to yield **28** (11.4 g; 74.6 %) as a pure oil, mp 124-125 $^oC$ (from diisopropyl ether). IR (KBr): 2950, 2840, 2830, 2250, 1580, 1430, 1350, 1280, 1180, 1160 $cm^{-1}$. Anal. Calcd for $C_{22}H_{24}N_4O_4S$: C, 59.98, H, 5.49, N, 12.72, S, 7.28. Found: C, 60.02, H, 5.51, N, 12.71, S, 7.25.

**4-Amino-5,5-diethoxy-1-(toluene-4-sulfonyl)-3,4-dihydro-1*H*-benzo[*c,d*]indole** (**29**) To a cold solution (0 $^oC$) of **28** (9.4 g; 21.2 mmol) in dry THF (0.5 L) LAH (9.0 g; 237 mmol) was added in portion wise during about 10 min. The reaction mixture was stirred at rt for 3 h, then the mixture was cooled again with an ice-bath and water (200 mL) was added in dropwise during about 0.5 h. The resulting precipitate was filtered off, washed with $CHCl_3$ (200 mL) and the organic solvent was evaporated under reduced pressure. The residue was dissolved in a mixture of $CHCl_3$ (0.5 L) and water (0.3 L). After extraction the phases were separated and the organic phase was washed with water (2x0.3 L), dried ($Na_2SO_4$). The filtrate was evaporated under reduced pressure and the residue was purified by chromatography (Merck 9385, eluent: $CHCl_3$; $CHCl_3$ – MeOH, 200/1) to yield **29** (7.96 g; 90.0 %) as a pure oil. IR (KBr): 3380, 2890, 2950, 1590, 1430, 1345, 1280, 1160 $cm^{-1}$. MS (*m*/*z*, %): 414 (80, $M^+$), 400 (9), 385 (62), 369 (25), 339 (78), 323 (33), 259 (18), 230 (26), 213 (82), 183 (100), 167 (45), 155 (48). Anal. Calcd for $C_{22}H_{26}N_2O_4S$: C, 63.75, H, 6.32, N, 6.76, S, 7.73. Found: C, 63.71, H, 6.29, N, 6.69, S, 7.71.

**4-*N*-(Formyl)amino-5,5-diethoxy-1-(toluene-4-sulfonyl)-3,4-dihydro-1*H*-benzo[*c,d*]indole** (**30**) To a solution of **29** (7.1 g; 17.0 mmol) in diisopropyl ether (50 mL) ethyl formate (20.5 mL; 255 mmol) was added and the reaction mixture was stirred at 60 $^oC$ for 48 h. After cooling, the solvent was evaporated under reduced pressure and the residue was crystallized from a mixture of ether and diisopropyl ether (75 + 25 mL) to yield **30** (6.13 g; 83.8 %) as crystals, mp 164-165 $^oC$. IR (KBr): 3250, 3040, 2950, 2900, 2860, 1670, 1640, 1595, 1540, 1430, 1170, 1160 $cm^{-1}$. MS (*m*/*z*, %): 442 (8, $M^+$), 396 (21), 367 (100), 352 (80), 339 (32), 324 (7), 241 (19), 213 (9), 197 (9), 184 (36). Anal. Calcd for $C_{23}H_{26}N_2O_5S$: C, 62.43, H, 5.92, N, 6.33, S, 7.24. Found: C, 62.39, H, 5.89, N, 6.29, S, 7.26.

**4-*N*-(Methyl)amino-5,5-diethoxy-1-(toluene-4-sulfonyl)-3,4-dihydro-1*H*-benzo[*c,d*]indole** (**31**) To a solution of **30** (884 mg; 2.0 mmol) in THF (15 mL) LAH (250 mg; 6.6 mmol) was added in portion wise at 55-60 $^{o}$C during about 15 min. The reaction mixture was stirred at the above temperature for 2 h, then was cooled with an ice-bath. The excess of the reagent was decomposed with ethyl acetate (5.0 mL), then water (5.0 mL). To the mixture silica (2.0 g) was added and the mixture was evaporated under reduced pressure. The residue was purified by column chromatography (Merck 9385, eluent: hexane; hexane – ethyl acetate, 75/25; hexane – ethyl acetate – $CH_2Cl_2$, 75/25/5) to yield **31** (492 mg; 59.0 %) as a pure oil. IR (KBr): 3300, 2800, 1600, 1430, 1370, 1290, 1120 cm$^{-1}$. Anal. Calcd for $C_{23}H_{28}N_2O_4S$: C, 64.46, H, 6.59, N, 6.54, S, 7.48. Found: C, 64.51, H, 6.54, N, 6.50, S, 7.31.

**4-[*N*-(Methyl)-*N*-propargyl]amino-5,5-diethoxy-1-(toluene-4-sulfonyl)-3,4-dihydro-1*H*-benzo[*c,d*]-indole** (**32**) To a solution of **31** (856 mg; 2.0 mmol) in acetone (30 mL) dry $K_2CO_3$ (1.0 g; 7.25 mmol) and propargyl bromide (1.0 mL; 8.9 mmol) were added and the reaction mixture was stirred at 60 $^{o}$C for 12 h. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was dissolved in a mixture of $CHCl_3$ (100 mL) and water (20 mL). The organic phase was washed with water (3x10 mL), dried ($Na_2SO_4$). The filtrate was evaporated under reduced pressure to yield **32** (909 mg; 97.1 %) as a pure oil which could be used without further purification in the next experiments. An analytical sample was purified by column chromatography (eluent: hexane – ethyl acetate, 7/3) to yield a colorless oil. IR (KBr): 3450, 3200, 2950, 2880, 1600, 1450, 1375, 1180 cm$^{-1}$. MS (*m*/z, %): 466 (17, $M^+$), 437 (100), 420 (24), 391 (9), 375 (15), 352 (8), 311 (23), 281 (6), 243 (25), 220 (22), 197 (48). Anal. Calcd for $C_{26}H_{30}N_2O_4S$: C, 66.93, H, 6.48, N, 6.00, S, 6.87. Found: C, 66.98, H, 6.44, N, 6.07, S, 6.85.

**4-(*N*-Formyl)amino-1-(toluene-4-sulfonyl)-3,4-dihydro-1*H*-benzo[*c,d*]indol-5-one** (**33**) and (**30**) The formylation of **29** was performed with mixed anhydride as described above in the preparation of **23** [acetic anhydride: 0.3 mL; 3.12 mmol; formic acid: 0.15 mL; 3.12 mmol; **29**: 1.0 g, 2.4 mmol]. The crude product was purified by column chromatography (Merck 9385, eluent: $CHCl_3$ – hexane – MeOH, 100/10/1). In the course of the chromatography two components were separated.

Compound (**30**) (225 mg, 22 %): spectroscopic data, see above.

Compound (**33**) (606 mg, 71.0 %): mp 148-154 $^{o}$C (form ether). IR (KBr): 3380, 3280, 1680, 1670, 1640, 1600, 1435, 1300, 1175 cm$^{-1}$. MS (*m*/z, %): 323 (100), 183 (10), 155 (57), 140 (8). Anal. Calcd for $C_{18}H_{16}N_2O_4S$: C, 60.66, H, 4.53, N, 7.86, S, 9.00. Found: C, 60.64, H, 4.51, N, 7.81, S, 8.95.

**4-*N*-(Acetyl)amino-5,5-diethoxy-1-(toluene-4-sulfonyl)-3,4-dihydro-1*H*-benzo[*c,d*]indole** (**34**) In an other run compound (**29**) (3.84 g; 10.0 mmol) was allowed to react with mixed anhydride as described above. The crude product was recrystallized from diisopropyl ether to yield **34** (3.93 g; 91.4 %), mp 97-

98 °C. IR (KBr): 3400, 2980, 2900, 2880, 1650, 1590, 1500, 1430, 1350, 1280 $cm^{-1}$. Anal. Calcd for $C_{24}H_{28}N_2O_5S$: C, 63.14, H, 6.18, N, 6.14, S, 7.02. Found: C, 63.09, H, 6.21, N, 6.21, S, 7.00.

**4-(*N*-Acetyl)amino-1-(toluene-4-sulfonyl)-3,4-dihydro-1*H*-benzo[*c*,*d*]indol-5-one** (**35**) To a solution of **34** (3.0 g; 6.57 mmol) in acetone (100 mL) HCl solution (1N, 20 mL) was added at rt and stirred for 3 h. The organic solvent was evaporated under reduced pressure and the residue was poured into a mixture of $CHCl_3$ (300 mL) and aqueous saturated $NaHCO_3$ solution (30 mL). The phases were separated and the organic layer was washed with water (2x50 mL), dried ($Na_2SO_4$). The solvent was evaporated under reduced pressure and the residue was crystallized from a mixture of hexane and ethyl acetate (1/1, 50 mL) to yield **35** (2.15 g; 85.6 %), mp 196-197 °C. IR (KBr): 3350, 1695, 1640, 1520, 1440, 1360, 1300, 1175 $cm^{-1}$. MS (*m*/z, %): 382 (37, $M^+$), 339 (11), 323 (100), 227 (9), 185 (24), 155 (74), 129 (16). Anal. Calcd for $C_{20}H_{18}N_2O_4S$: C, 62.81, H, 4.74, N, 7.33, S, 8.38. Found: C, 62.76, H, 4.71, N, 7.19, S, 8.30.

**1-(Toluene-4-sulfonyl)-7-oxo-9β-hydroxy-1,4,5,6,7,8-hexahydroindolo[4,3-*ef*]indole (5β-H)** (**37**)
To a solution of LHMDS (0.9 mL; 1 mol/L, THF) at – 78 °C dry ethyl acetate (0.09 mL; 0.9 mmol) was added and the mixture was stirred at the above temperature for 15 min. Then a solution of **33** (267 mg; 0.75 mmol) in dry THF (10 mL) was admixed and the mixture was stirred for 15 min. To the mixture HCl solution (20 %, 2.0 mL) was added (pH ≈ 7) and the temperature was allowed to warm to rt. The organic solvents were evaporated under reduced pressure and the residue was dissolved in a mixture of $CHCl_3$ (30 mL) and water (10 mL). The organic phase was washed with water (10 mL), dried ($Na_2SO_4$). The solvent was evaporated under reduced pressure and the residue was purified by chromatography (eluent: $CHCl_3$ – acetone, 8/2) to yield **37** (70 mg; 24.0 %) as a pure oil, mp 227-228 °C (from ether). IR (KBr): 3400, 2950, 1680, 1600, 1435, 1350, 1300, 1165, 1110 $cm^{-1}$. MS (*m*/z, %): 382 (2, $M^+$), 325 (36), 277 (12), 231 (5), 170 (27), 155 (15), 132 (19), 115 (23), 105 (52). $^1$H NMR (400 MHz, $CDCl_3$ + DMSO-$d_6$), δ: 2.36 (3H, s, Ts-Me), 2.71 (1H, d, *J*= 14.8 Hz, H-$8_A$), 2.79 (1H, d, *J*= 14.8 Hz, H-$8_B$), 2.89 (1H, dd, *J*= 16.8 + 5.5 Hz, H-$4_A$), 3.16 (1H, dd, *J*= 16.8 + 4.9 Hz, H-$4_B$), 4.01 (1H, dd, *J*= 5.5 + 4.9 Hz, H-5), 5.68 (1H, s, OH), 7.22 (1H, br s, NH), 7.26 (1H, bs, H-2), 7.27 (2H, m, Ts-*m*-CH), 7.37 (1H, dd, *J*= 7.6 + 7.2 Hz, H-12), 7.41 (1H, d, *J*= 7.2 Hz, H-11), 7.77 (2H, m, Ts-*o*-CH), 7.79 (1H, d, *J*= 7.6 Hz, H-13). $^{13}$C NMR (100 MHz, $CDCl_3$ + DMSO-$d_6$), δ: 20.49 (Ts-Me), 22.78 (C-4), 44.86 (C-8), 59.63 (C-5), 73.51 (C-9), 111.39 (C-13), 114.75 (C-3), 119.53 (C-11), 119.61 (C-2), 125.04 (C-12), 125.74 (Ts-*o*-CH), 127.08 (C-15), 129.00 (Ts-*m*-CH), 131.84 (C-10), 132.59 (C-14), 134.12 (Ts-C1'), 144.07 (Ts-*p*-C), 173.48 (C-7). Anal. Calcd for $C_{20}H_{18}N_2O_4S$: C, 62.81, H, 4.74, N, 7.33, S, 8.38. Found: C, 62.90, H, 4.77, N, 7.29, S, 8.35.

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