Cascade Reaction of Camphor-Derived Diynes with Transition Metal Compounds

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Platinum(II) catalyzes the isomerization of camphor sulfonamide diynes in a cascade reaction involving annulation of a five-membered ring to the camphor skeleton, ring-enlargement by C-C bond cleavage, reduction of sulfur(VI) to sulfur(IV), and oxidation of a hydroxy group to a ketone. The reactions of the diynes with other transition metal compounds were also studied. Copper, gold and rhenium give final products similar to those obtained with simple Brønsted acids or halogens, mainly by annulation of a five-membered ring to the camphor moiety, accompanied by reduction of a sulfonamide to a sulfinamide group, but lacking the ring-enlargement step. Palladium(II) occupies an intermediate position as both types of products are obtained. The reaction mechanism and intermediates are discussed.

Introduction

Functional groups may strongly deviate from their textbook behaviour when they are crowded together. We have shown this for the combination of two alkynes with a sulfonamide and a hydroxy group which are held in close vicinity at a camphor skeleton, as in compound 2a (Fig. 1) [1]. Sulfonamide reduction induced by treatment with acids or halogens was an unexpected consequence [2]. When we used TiCl₄ as reagent, [1] 2a showed a different regioselectivity from that found with HCl [2], although the overall reaction was the addition of HCl to 2a in both cases. In contrast, camphor derivatives not containing triple bonds form the expected coordination compounds [3 – 5]. We therefore decided to explore in more detail the reactivity of such camphor-derived diynes with transition metal compounds. In addition to the phenyl derivative 2a, we also studied the butyl compound 2b which we obtained from 1 by reaction with the lithium salt of 1-hexyne, together with the monosubstituted compound 3.

Results and Discussion

The reaction of non-terminal alkynes with transition metal compounds in lower oxidation states normally leads to π-coordination to the triple bond, forming stable complexes with e.g. platinum in analogy to the better known alkene complexes [6 – 9]. Platinum(IV) catalyzes the hydration of triple bonds to ketones which may then undergo further reactions by the action of acids [10]. In our compound 2, however, two alkyne groups are held in close vicinity to a sulfonamide and a hydroxy group. This unique combination modifies the reaction pattern completely, not only towards halogens and acids, but also towards transition metal compounds, and no π-complexes are observed.

With respect to their reactivity towards diynes 2a and 2b, the transition metal compounds studied may be divided into three groups, besides those which did not react at all (RhCl₃, RuCl₃, AgCl and [IrCl(CO)(PPh₃)₂], the last one neither thermally nor photochemically). The first group induces a new reaction pattern, leading to a ring enlargement in
the camphor skeleton. The second group consists of transition metal compounds which behave like simple Brønsted acids such as HCl or oxidizing agents like I₂. The third group allows for the detection of transition metal complexes containing the diyne 2a or its derivatives.

**Ring enlargement by platinum salts**

In dichloromethane or chloroform PtCl₂ or [PtCl₂(NCPh)₂] react with camphor-derived diynes 2 leading to the formation of 4 with just a slight contamination by compound 7 (Fig. 1). In these processes no metal complexes can be detected not even as intermediates. As no suitable crystals for X-ray diffraction analysis of compounds 4 could be grown, the structure elucidation relies mainly on NMR spectroscopy. Mass spectrometry shows that the compounds are isomers of the starting materials 2. The highly asymmetric enamide group with an extreme charge distribution resonates at δ_C = 165.6 (160.5) for C-2 and 107.1 (109.5) for C-3 (values in brackets are for 4b). For the structural assignment, the most important crosspeaks in the long-range CH correlation were from H-5 to C-4 and C-3, and from H-10 to C-2. The only structure consistent with this pattern is 4, thus suggesting the cleavage of the bond between C-2 and C-3 in the original camphor skeleton of 2. The assignment was further confirmed by NOE measurements (ROESY) for both compounds.
(values for 4b in brackets) which showed crosspeaks between the methyl group (12-H) and the exoprotons 8-H ($\delta_H = 2.13$ (2.05) ppm) and 9-H ($\delta_H = 1.98$ (2.12)), and the syn-proton (close to the methyl group) 10-H ($\delta_H = 3.58$ (3.38)). Particularly revealing is the crosspeak between the olefinic proton H-5 and the endo-H-8 ($\delta_H = 1.85$ (1.94)). The structure of the ring-enlarged system was thus completely established by NMR methods. It is interesting to note that the tricyclic system has some features of taxoid compounds, in particular the eight-membered ring containing the dimethylmethylene bridge. As the starting materials 2 and the products 4 are isomeric, one can compare their energy content directly. Semi-empirical calculations with the PM3 Hamiltonian gave optimised structures (Fig. 3) for 2a and 4a, with the corresponding heats of formation being 52.5 kcal/mol for 2a and –18.9 kcal/mol for 4a. This means that the products are about 70 kcal/mol more stable than the starting materials, a result which can be explained by the high energy content of the triple bonds which is released during the reaction. The formation of the products 4 is therefore thermodynamically highly favoured and should proceed rapidly when a suitable catalyst is added.

We therefore checked the possibility to induce ring enlargement under catalytic conditions using 10 mol% of [PtCl$_2$(NCPH)$_2$] (the benzonitrile complex was used for solubility reasons and allowed to follow the reaction in a NMR tube). Indeed, after 20 days for 2a or 2 days for 2b, the starting materials were completely consumed and the products 4 obtained with turnover numbers of ca. nine per mole. No intermediates could be detected during the reaction period by NMR; the only significant change (besides the appearance of product signals) is the broadening of the signal of the OH group and the detection of non-coordinated benzonitrile. Based on the knowledge on the reactivity of such camphor-derived diynes with halogens, acids, and other transition metal compounds, we suggest a catalytic cascade reaction mechanism with the following steps:

1. Coordination of platinum(II) to the hydroxy group of 2, liberating a molecule of benzonitrile and a proton. This step can be seen in proton NMR.
2. Attack of the proton at the vicinal carbon atom of the triple bond which turns into a double bond. The bending introduced by the sp$^2$ carbon atoms brings them in a suitable position to the remaining triple bond, thus inducing carbon-carbon bond formation and annulation of a five-membered ring to the camphor skeleton.
3. Stabilization of the intermediate carbocation by bond formation to one of the oxygen atoms of the SO$_2$ group, transferring the positive charge to sulfur.
4. In contrast to the situation in the cation obtained in the reaction with trifluoroacetic acid [2], the sulfur-stabilized cation is a zwitterion, and no strong nucleophile is present in the reaction mixture. Thus, cleavage of the platinum-oxygen bond results in oxidation of the former hydroxy group to a keto group. Simultaneously the adjacent C-C bond breaks and an enamide type C-C double bond is formed. Stereoselective reduction of the sulfonamide to a sulfonamide accompanied by the formation of an exocyclic keto group completes this step.
5. Recombination of the [PtCl$_2$(NCPH)] fragment with benzonitrile regenerates the catalyst.

Transition metal compounds with acidic or oxidizing character

Among the transition metal compounds used as starting materials, those with considerable Lewis acidity simply react with the compounds 2 under formation of polymeric products. This is the case with Ag[BF$_4$] and [Ir(CO)(PPh$_3$)$_2$][BF$_4$], generated in situ from Vaska’s complex and Ag[BF$_4$]. On the other hand Brønsted acids like HCl or CF$_3$CO$_2$H react with the diyne 2a under annulation of a five-membered ring to the camphor moiety, accompanied by reduction of the sulfonamide group to a sulfonamide [2]. This reaction occurs via a sulfur-stabilized cation as intermediate which is stable in trifluoroacetic acid solution, but not in other solvents. K[ReO$_4$] in methanol does not react with 2a but, on addition of aqueous HCl, the cation 5 (Fig. 2) is formed as a perrenate salt which remains stable in methanolic solution and is characterized by NMR ($^1$H and $^{13}$C spectrum identical to the cation in trifluoroacetic acid) and ESI-MS (both cation and anion were found). Attempts to isolate the pure compound gave always mixtures with the starting material 2a. The formation of the cation can readily be explained in analogy to the reaction with Brønsted acids, i.e. protonation at the triple
bond, followed by annulation of a five-membered ring to the camphor skeleton, and stabilization of the cation by transfer of the positive charge to the sulfur atom [2]. The anion $[\text{ReO}_4^-]$ obviously has a stabilizing effect on the cation since with other counterions attempts to isolate a salt of the cation 5 were never successful; decomposition to either intractable mixtures of polymers or to compounds like 7 - 10 instead occurred [2].

In contrast to perrhenate, mercury(II) acts rather as an oxidizing agent such as iodine. A solution of 2a in methanol reacts with Hg(OAc)$_2$ to give the acetate 6 as the main product which was earlier obtained with iodine and characterized by crystal structure analysis. As a by-product, the hydroxy compound 7 was also obtained (Fig. 2).

A plausible reaction mechanism involves the classical attack of a mercury(II) compound at a triple bond, in the same position where a proton attacks in the case of perrhenate. This intermediate then undergoes a cyclization to a sulfur-stabilized cation of the type 5. In this case, it still contains mercury bound to the former acetylenic carbon atom and has an acetate as counterion. When the reaction is run in an NMR tube with CD$_2$OD as solvent, there are indeed signals in the NMR spectrum which are similar to those observed for the cation 5 in the perrhenate case, although badly resolved. These signals disappear during the reaction and are replaced by the signals of the final product 6, with simultaneous precipitation of metallic mercury.

Transition metal complexes derived from the diynes

In contrast to the transition metals mentioned above, in the reactions of CuCl$_2$, FeCl$_3$-6H$_2$O or [AuCl(Me$_2$S)] with 2a no organic products were directly observed. Instead the formation of the complexes [CuClL] I or [FeClL$_2$(H$_2$O)$_2$] II (formulated according to microanalysis) was detected. The reaction of 2a with PdCl$_2$ corresponds to an intermediate situation since 4a is formed in addition to the complex [PdClL] III. Due to the paramagnetic character of all the complexes but that derived from gold we can not state whether the coordinated ligand L corresponds to unchanged 2a or one of its derived form. In order to try to ascertain the nature of the complexes they were destroyed and the liberated organic species analysed.

From the reaction of complex I with aqueous KCN compounds 7 and 8 (Fig. 2) were identified by NMR. In addition to coordination to nitrogen...
and/or oxygen, copper(II) reacts here as an oxidizing agent. The only difference between 7 and 8 is the stereochemistry at sulfur. Compound 7 is the original product obtained from the sulfur-stabilized cation while inversion of the configuration at sulfur is observed in the presence of acids. It seems plausible that in this case it is the copper centre that acts as a Lewis acid and inverts the configuration.

No organic products other than 2a were detected on destroying the iron complex II. Moreover, the complex is non-conducting in CH2Cl2 solution (\(\lambda_M = 8 \Omega^{-1} \text{cm}^2 \text{mol}^{-1}\)), and the study made by cyclic voltammetry suggests that the metal is Fe(III) (E1/2\text{red} = -0.08 V), well in the potential region of the related iron(III) complexes [FeCl₂L₂]⁺ (L = camphor derivative, E = 0.08 - 0.10 V) [3, 5]. It thus seems plausible that the coordination of the ligand to the iron centre involves deprotonation of the NH or the OH groups with no further modifications.

Treatment of the palladium complex III with aqueous Na₂CO₃ affords a mixture of 7, 9, and 10 (Fig. 2) as identified by NMR spectroscopy. The products are also observed in the reaction of 2a with I₂ or HCl.

Precipitation of gold accompanies the reaction of 2a with [AuCl(Me₂S)], and no reliable elemental analysis could be obtained for the complex which on the basis of NMR seems to coordinate a ligand (with a spectrum similar to species 7). Further but slow precipitation of gold continues on standing of the CDCI₃ solution. When it finishes after four days, compounds 8 and 10 are found as organic products (Fig. 2). This suggests that during the reaction HCl has been liberated from the complex which partially formed the cation of 5. This was then attacked nucleophilically by chloride to give 10. As mentioned before, 8 is formed from the original product 7 (which might be present as a ligand in the intermediate gold complex) by acid-induced inversion of the configuration at sulfur induced by acids.

**Conclusion**

Platinum(II) catalyzes the isomerization of the camphor-derived diynes 2 to new heterocycles 4 in a cascade reaction involving annulation of a five-membered ring to the camphor skeleton, C-C bond cleavage leading to ring enlargement, oxidation of a hydroxy group to a ketone, and reduction of a sulfonamide to a sulfonamide. Palladium(II) produces the same compound, but with other byproducts. All other metal compounds studied react similarly to halogens or acids, leading mainly to oxidized products having the first steps in common with the platinum(II)-catalyzed reaction, but lacking the C-C bond cleavage leading to ring enlargement and the oxidation of the hydroxyl group to the ketone. The products 4 have some structural features present in taxoids, such as the eight-membered ring with a dimethylmethylene bridge. The easy access to such enantiomERICally pure compounds from camphor by a catalytic reaction with platinum(II) may therefore be an interesting entrance into new structural variants of potential anti-cancer drugs.

**Experimental Section**

**General remarks:** NMR spectra were obtained with Bruker AM 360 (1H: 360.13 MHz, 13C: 90.56 MHz) and Varian Unity 300 (1H: 299.95 MHz, 13C: 75.43 MHz) instruments. For the assignment of the signals, DEPT, COSY, ROESY, HMQC, and long-range C-H-correlation (BIRD-TRAP [11]) have been used. The numbering of the carbon atoms and attached hydrogen atoms is indicated in Fig. 1. IR spectra were obtained with a Perkin Elmer 683 spectrophotometer. Optical rotations were measured with a Perkin Elmer 241 M polarimeter. [a]-values are given in \(10^{-1} \text{deg cm}^{-2} \text{g}^{-1}\). Mass spectra were measured with Varian CH5 (EI mode, 70 eV) and LCQ Finnigan (ESI) instruments. Conductivity was measured with a CG 855 Schott conductometer using a LF 1100 Schott cell. Electrochemical studies were performed with an EG&G PAR 173 potentiostat and an EG&G PARC 175 universal programmer, using a 0.2 molar solution of [NBu₄][BF₄] / THF and a platinum wire as working electrode. Potentials were measured at 200 mVs⁻¹, using the ferrocene / ferrocinium redox couple as internal standard (E₁/₂ = 0.54 V vs. SCE). Semiempirical calculations were performed with the program GAMESS(US) [12] using the PM3 Hamiltonian in the standard parametrization. Calculation of the Hessian matrix at the optimized geometries did not show any imaginary frequencies, indicating that true minima were obtained.

**Synthesis of the starting materials**

The synthesis of the phenyl diyne derivative 2a has already been described [1].
To a solution of 1-hexyne (1.68 g, 20.4 mmol) in dry diethyl ether (50 cm³) under nitrogen butyl lithium (20.5 mmol, 8.2 cm³ of 2.5 M solution in hexane) was added dropwise with stirring. To the suspension thus obtained the oxoimine 1 (2.27 g, 10.0 mmol) was added. An exothermic reaction was observed. Stirring was continued for 12 h, and water (100 cm³) was added to the yellow suspension. The etheral layer was separated, dried (Na₂SO₄), and the solvent was evaporated to give the monohexyne derivative 3 which was purified by filtration of a dichloromethane solution (50 cm³) over silicagel (20 g). After evaporation of the solvent, the residue was dried under vacuum and recrystallized from dichloromethane / hexane) was added dropwise with stirring.

Reactions with metal salts

Reaction of 2a with K[ReO₄]/HCl

To a suspension of K[ReO₄] (100 mg, 0.35 mmol) and 2a (500 mg, 1.16 mmol) in methanol (50 cm³), aqueous HCl (0.5 cm³, 6.0 mmol) was added under nitrogen and the mixture stirred for 2 h. The yellow solution was concentrated to 15 cm³ and the bulk of unreacted 2a was filtered off. The solvent was evaporated under vacuum, the residue extracted with diethyl ether and then dried under vacuum. It consists of a ca. 1:1 mixture of starting material 2a and a product which was identified by NMR and mass spectroscopy as the perrenate 5. The product decomposes slowly when dissolved in CDCl₃, but is stable for at least 5 d in CD₂OD solution and was characterized by ¹H and ¹³C NMR. The cation is identical with that obtained when 2a is dissolved in CF₃CO₂H [2], and both cation and anion were found by ESI-MS (in CD₃OD): cation: 432 (C₂₆H₂₆NO₃S⁺), anion: 249, 251 ([ReO₄⁻]). It was not possible to obtain 5 without contamination with 2a. The microanalytical data support a ca. 1:1 mixture of 2a and 5

C₃₂H₅₁N₂O₁₀Re₂S₂ (1113.2)
Calcd C 56.1 H 4.6 N 2.5 S 5.8%,
Found C 55.2 H 5.0 N 2.4 S 5.6%.

Reaction of 2a with CuCl₂

Anhydrous CuCl₂ (90 mg, 0.67 mmol) and 2a (300 mg, 0.70 mmol) were suspended in dichloromethane (20 cm³) under nitrogen and stirred at room temperature for 2 d. After filtering off unreacted CuCl₂, the solvent was removed in vacuum and the residue extracted with diethyl ether (3 × 10 cm³). The remaining solid was dried under vacuum and recrystallized from dichloromethane / diethyl ether. The NMR spectra show badly resolved signals due to paramagnetism and suggest the presence of at least two different ligands. IR spectrum (KBr): ν 1760 (m), 1715 (s), 1705 (s), 1655 (s),
1645 (s), 1590 (s), 1570 (m), 385 (m). The microanalytical data show the presence of Cu:Cl:ligand in the ratio 1:1:1 where “ligand” may be a mixture of reaction products of 2a.

C26H25ClCuNO3S (530.0)
Calcd C 58.9 H 4.8 N 2.6 S 6.0%,
Found C 60.3 H 5.4 N 2.5 S 5.8%.

After treatment of the solid with 10% aqueous KCN solution and extraction with dichloromethane, two products were obtained in the ratio 4:1, the main product being (2S,3aS,6aS,9aS)-9-benzyol-6a-hydroxy-10,10-dimethyl-8-phenyl-3a,4,5,6,6a,7-hexahydro-1H,3H-3a,6-methano-indeno[3a,4-c]isothiazol-7-one 2-oxide (7) and the byproduct (2R,3aS,6aS,9aS)-9-benzyol-6a-hydroxy-10,10-dimethyl-8-phenyl-3a,4,5,6,6a,7-hexahydro-1H,3H-3a,6-methano-indeno[3a,4-c]isothiazol-7-one 2-oxide (8). Both compounds have already been obtained in the reaction of 2a with iodine [2].

Reaction of 2a with FeCl3

To a solution of FeCl3·6H2O (100 mg, 0.37 mmol) in THF (12 cm3) 2a (320 mg, 0.74 mmol), was added and the solution was stirred under nitrogen for 2 d. The precipitate was filtered off and the solvent evaporated under vacuum. The oily residue was washed with diethyl ether (2x5 cm3) and dried under vacuum, yield 110 mg (30%). IR spectrum (KBr): ν 3390 (m), 3310 (m), 1645 (s), 1595 (w), 380 (br). The paramagnetic compound contains Fe:Cl:ligand in the ratio 7:3 and identified by X-ray crystallography [2]. As a byproduct (ca. 10% yield), (2S,3aS,6aS,9aS)-9-benzyol-6a-hydroxy-10,10-dimethyl-8-phenyl-3a,4,5,6,6a,7-hexahydro-1H,3H-3a,6-methano-indeno[3a,4-c]isothiazol-7-one 2-oxide (6) which has already been obtained by the reaction of 2a with iodine and characterized by X-ray crystallography [2].

Reaction of 2a with [AuCl(Me2S)]

To a solution of 2a (129 mg, 0.3 mmol) in 10 cm3 of CH2Cl2, [AuCl(Me2S)] (88 mg, 0.3 mmol) was added. After stirring for 2 h, the brown precipitate (Au) was filtered off. The filtrate was concentrated to ca. 2 cm3, cyclohexane (5 cm3) was added, and the mixture kept at -30 °C for 16 h. After filtering off unreacted [AuCl(Me2S)], the solution was left evaporating in air. The remaining yellow powder (110 mg) is stable as a solid, but precipitates metallic Au when standing in polar solutions for at least one hour. δH (CDCl3): 1.04, 1.73 (2×s, 3H each, H-9, H-10), 1.44 (s, 12H, cyclohexane), 2.29 (d, 1H, J 4.8, 4-H), 3.88 (d, 1H, J 14.0, 8-H), 2.66 (dd, 1H, J1 14.0, J2 6.0, 8-H), 1.50 - 2.10 (m, 4H, 5-H, 6-H), 7.16 (m, 4H), 7.30 (m, 4H), 7.69 (m, 2H). Neither NH nor OH were detected. When the precipitation of gold from the solution was finished after 4 days, two products were observed by 1H- and 13C-NMR in the ratio 7:3 and identified as (2R,3aS,6aS,9aS)-9-benzyol-6a-hydroxy-10,10-dimethyl-8-phenyl-3a,4,5,6,6a,7-hexahydro-1H,3H-3a,6-methano-indeno[3a,4-c]isothiazol-7-one 2-oxide (8) and (2R,3aS,6aS,7S,9aS)-9-benzyol-7-chloro-6a-hydroxy-10,10-dimethyl-8-phenyl-3a,4,5,6,6a,7-hexahydro-1H,3H-3a,6-methano-indeno[3a,4-c]isothiazole 2-oxide (10) which was also obtained by the reaction of 2a with iodine or HCl [2].

Reactions of compound 2 with [PtCl2(NCPh)2]

The compound 2a or 2b (0.14 mmol) was dissolved in 0.7 cm3 of CDCl3 in a NMR tube, and [PtCl2(NCPh)2] (8 mg, 0.017 mmol) was added. The reaction was monitored by NMR spectroscopy. In the case of 2a as starting material, the reaction was complete after 20 days and the reaction mixture consisted of the product 4a (90%) ((2S,3aS)-10-benzyol-11,11-dimethyl-9-

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phenyl-3,3a,4,5,6,7-hexahydro-1H-3a,6-methanocyclonona[c]isothiazol-7-one 2-oxide) and a byproduct (10%) which was identified by NMR spectroscopy as (2S,3aS,6aS,9aS)-9-benzoyl-6a-hydroxy-10,10-dimethyl-8-phenyl-3a,4,5,6,6a,7-hexahydro-1H,3H-3a,6-methano-indeno[3a,4-c]isothiazol-7-one (7), a compound previously obtained in the reaction of 2a with iodine [2]. When a 2:1 ratio of 2a to Pt complex was used (43 mg of 2a and 23 mg of [PtCl₂(NCPh)₂]), the starting material was consumed already after 7 days, but the mixture consisted of product and byproduct in the ratio 1:1. In the case of 2b as starting material, the reaction was complete after 2 days with a catalytic amount of [PtCl₂(NCPh)₂], and 4b was the only product. In all cases, the products were isolated by chromatography on silicagel. 4a: dichloromethane / diethyl ether 1:1, Rf 0.2 4b: dichloromethane / acetone 10:1, Rf 0.6.

**Reaction of 2a with PtCl₂**

A suspension of PtCl₂ (100 mg, 0.375 mmol) and 2a (350 mg, 0.81 mmol) in dichloromethane (30 cm³) was stirred for 4 days. After filtering off the PtCl₂, the solution was concentrated to 2 cm³. Diethyl ether (1 cm³) was added and the solution kept at −18 °C overnight. The microcrystalline yellow compound (4a) was filtered off. Yield 150 mg (43%).

**4a:** M.p. 270 °C (dec.), [α]D²⁰ −19.0 (c 0.5 in CH₂Cl₂).

C₂₆H₂₅NO₃S (431.6)

Calcd C 72.4 H 5.8 N 3.2%,

Found C 72.0 H 5.7 N 2.9%.

δH (CDCl₃): 1.35, 1.42 (2 × s, 3H each, H-12, H-13); 1.85, 2.13 (2 × m, 1H each, H-8); 1.98, 2.75 (2 × m, 1H each, H-9); 2.68 (d, 1H, J 5.5, H-7); 3.17, 3.58 (2 × d, 1H each, J 14.4, 10-H); 6.24 (s, 1H, 5-H); 6.80 (d, 2H, J 7.0, arom.); 7.15 (m, 7H, arom.); 7.23 (m, 1H, arom.); 12.48 (s, 1H, NH). δc (CDCl₃): 21.8, 28.6 (C-12, C-13); 25.3, 35.3 (C-8, C-9); 46.8 (C-10); 59.9 (C-11); 61.6 (C-6); 66.4 (C-7); 107.1 (C-3); 129.7 (C-5); 138.0 (C-4); 165.6 (C-2); 199.2 (C-14); 209.8 (C-6); 126.7, 127.0, 127.5, 128.3 (arom. o,m-CH); 127.7, 130.2 (arom. p-CH); 140.8, 141.6 (arom. C₉).

**4b:** oil, [α]D²⁰ +136.7 (c 1.2 in CH₂Cl₂).

C₂₂H₃₃NO₃S (391.6)

Calcd C 67.5 H 8.5 N 3.6%,

Found C 67.4 H 8.3 N 3.3%.

δH (CDCl₃): 0.85, 0.89 (2 × t, 3H each, J 7.4, 18-H, 22-H); 1.14, 1.22 (2 × s, 3H each, 12-H, 13-H); 1.10 (m, 2H, 17/21-H); 1.35 (m, 2H, br, 17/21-H); 1.28, 1.45 (2 × m, 2H each, 16/20-H); 1.94, 2.05 (2 × m, 1H each, 8-H); 2.12, 2.62 (2 × m, 1H each, 9-H); 2.04, 2.20 (2 × m, 1H each, 15-H); 2.32 (ddd, 1H, J 6.2, J 8.5, J 14.4, 19-H); 2.49 (m, 1H, 19-H); 2.52 (m, 1H, 7-H); 3.02, 3.38 (2 × d, 1H each, J 14.4, 10-H); 6.11 (s, 1H, 5-H); 12.08 (s, 1H, NH). δc (CDCl₃): 13.7, 13.8 (C-18, C-22); 21.3, 28.5 (C-12, C-13); 22.2, 22.5 (C-17, C-21); 25.0 (C-8); 34.7 (C-9); 40.5 (C-19); 27.6, 30.1 (C-16, C-20); 39.6 (C-15); 47.3 (C-10); 59.7 (C-11); 60.8 (C-1); 66.0 (C-7); 109.5 (C-3); 129.7 (C-5); 137.6 (C-4); 160.5 (C-2); 204.5 (C-14); 209.3 (C-6).

**Reaction of 2a with PdCl₂**

To a suspension of PdCl₂ (50 mg, 0.28 mmol) in methanol (30 cm³), 2a was added (250 mg, 0.56 mmol). The mixture was stirred at 60 °C for 3 h. After cooling to room temperature, unre­acted PdCl₂ (20 mg) was filtered off and the solu­tion concentrated to about 1 cm³. Diethyl ether (2 cm³) was added whereupon an oil separated and then dried in vacuum, affording a yellow solid. IR spectrum (KBr): ν 1715 (m), 1705 (s), 1635 (vs), 1590 (m), 1570 (m). NMR was not possible due to paramagnetism. Microanalysis suggests the ratio Pd:C:ligand = 1:1:2 where “ligand” may be a mixture of reaction products of 2a.

C₅₂H₅₀Cl₂N₂O₂Pd₂S₂ (1003.9)

Calcd C 62.2 H 5.0 N 2.8 S 6.4%,

Found C 62.3 H 5.3 N 2.8 S 5.8%.

In the mother-liquor trace amounts of 4a were detected.

After treatment of the yellow solid with excess aqueous Na₂CO₃ and extraction with dichloromethane, the following compounds could be detected (2S,3aS,6aS,9aS)-9-benzoyl-6a-hydroxy-10,10-dimethyl-8-phenyl-3a,4,5,6,6a,7-hexahydro-1H,3H-3a,6-methano-indeno[3a,4-c]isothiazol-7-
one 2-oxide (7), (2R,3aS,6aS,7S,9aS)-9-benzoyl-7-chloro-6a-hydroxy-10,10-dimethyl-8-phenyl-3a,4,5,6a,7-hexahydro-1H,3H-3a,6-methano-indeno-[3a,4-c]isothiazole 2-oxide (10), and (3aS,6aS,9aS)-9-benzoyl-6a-hydroxy-10,10-dimethyl-8-phenyl-3a,4,5,6a,7-hexahydro-1H,3H-3a,6-methano-indeno-[3a,4-c]isothiazol-7-one 2,2-dioxide (9). The three last compounds were also obtained in the reaction of 2b with iodine or HCl [2].

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