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SYNTHESIS OF 5-SUBSTITUTED INDOLE DERIVATIVES. PART 4[1]: NARATRIPTAN FROM α-ANILINOACETALDEHYDE DIMETHYLACETAL BY $TiCl_4$-MEDIATED CYCLISATION

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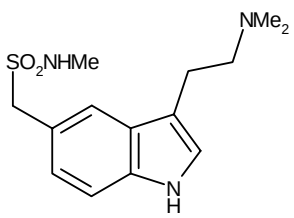
Abstract - *N*-Methyl-3-(1-methyl-4-piperidinyl)-1*H*-indole-5-ethanesulfonamide (Naratriptan, **2**) was prepared from *N*-methyl-*N*-phenylmethyl-2-(4-aminophenyl)-ethanesulfonamide (**3b**) through reductive alkylation with dimethoxyacetaldehyde followed by *N*-acylation and $TiCl_4$-mediated indolisation, according to Sundberg procedure. The isopropyl group proved to be a useful protecting group for sulfonate esters in a number of transformations but was cleaved in the presence of $TiCl_4$.

Among the serotonin (5-hydroxytriptamine, 5-HT) receptor subtypes, 5-HT_{1B} and 5-HT_{1D} are of particular interest because of the therapeutic potential of drugs acting at these sites. Sumatriptan (**1,** Scheme 1), a 5-$HT_{1B/1D}$ receptor agonist, was the first of a new class of therapeutic agents for the acute treatment of migraine headaches.[2] Its discovery has intensified research in this area and over the past years several related compounds, the so called 'triptans,' have entered the marketplace and late phase clinical trials. Among those, Naratriptan (**2**),[3] having an excellent overall bioavailability index, has been perharps the most successful.

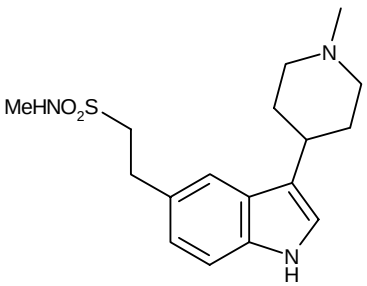
The key feature in the synthesis of Naratriptan is the introduction of the ethanesulfonyl moiety at the 5-position of indole. This is accomplished by the Heck-coupling of *N*-methylethenesulfonamide and 5-bromoindole in the industrial synthesis[3] of compound (**2**) in excellent yield. The following step, the electrophilic substitution at the 3-position of the indole, as the most characteristic feature of the

heterocycle, to attach the piperidine moiety,[3] also proceeds in yields over 80%. However, the use of Pd on industrial scale is a drawback of the synthesis, which might cause alternative synthetic pathways to emerge in the future.

Scheme 1



1



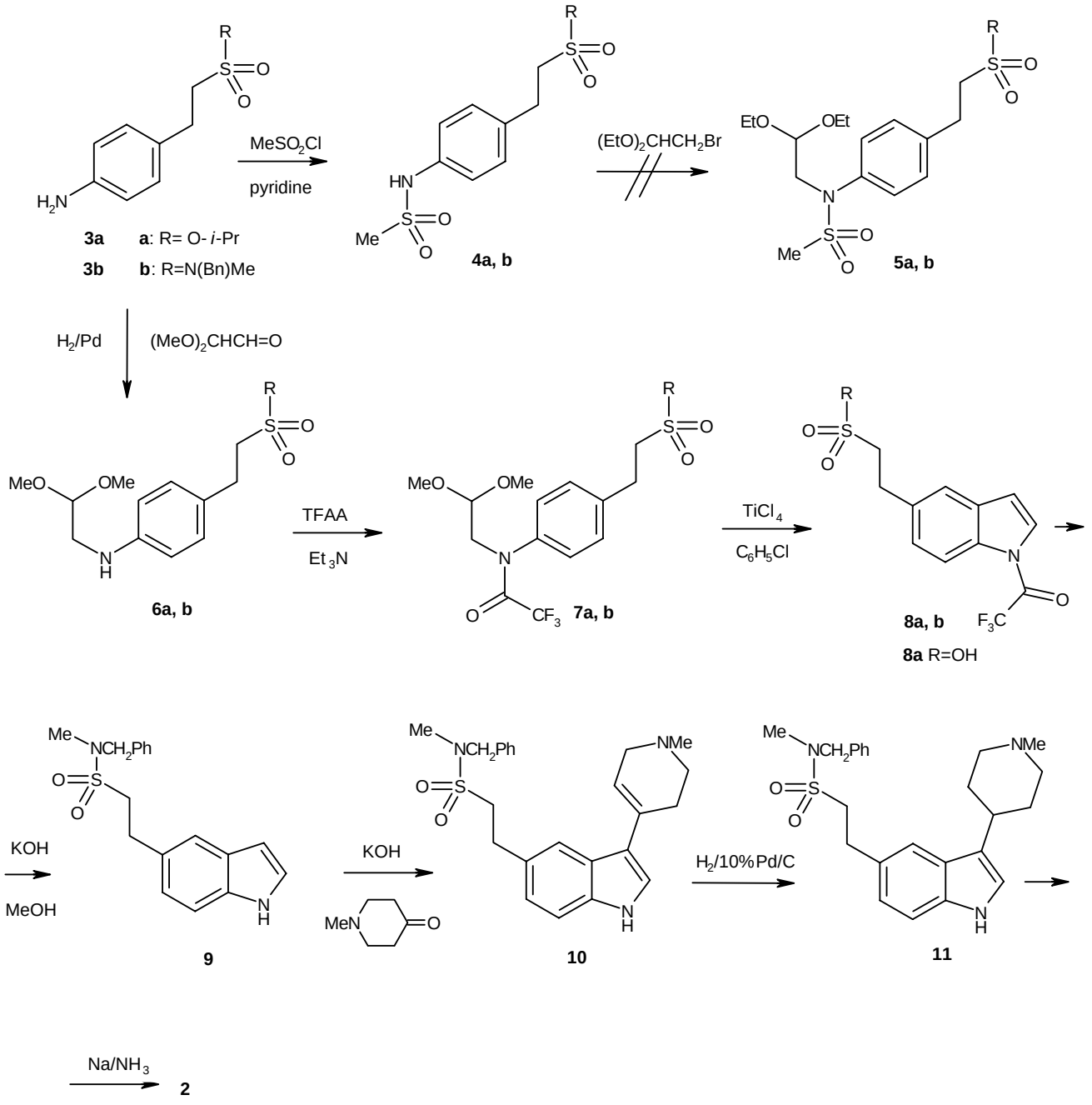
2

Synthesis of Naratriptan (2)

In this paper we want to report our results on the practical synthesis of compound (**2**) starting from 4-substituted aniline derivatives, according to Scheme 2. As a part of our ongoing research of the chemistry of indole-5-alkanesulfonic acids we have developed a practical synthesis of 2-(4-amino-phenyl)ethanesulfonic acid (**23**). This offered the possibility to synthesize compound (**2**) by traditional methods to obtain indoles. The Fischer synthesis did not seem attractive in this case as the Fischer indolisation of *N*-methyl-2-(4-hydrazinophenyl)ethanesulfonamide and (*N*-methyl-4-piperidino)-acetaldehyde furnished Naratriptan in a disappointingly low 30% yield.[3a]

The Nordlander[4] or Sundberg[5] type of indolisation offers an alternative route from anilines to indoles and is particularly suitable for 5-substituted indoles with electron-donor substituents. Sundberg method applies methanesulfonamides of (2,2-diethoxyethyl)anilines as starting materials for indoles and $TiCl_4$ to effect cyclisation, while Nordlander conditions involve heating *N*-(2,2-diethoxyethyl)trifluoroacetanilides in TFA-TFAA mixture. Alkylation of methanesulfonanilides or trifluoroacetanilides with bromoacetaldehyde diethylacetal was used to prepare the substrates for the ring closure.[4,5] The same alkylation of methanesulfonanilides (**4a, b**) to yield **5a**, **b** failed in our case using either Nordlander conditions ($NaHCO_3$ in EtOH, 80 ^oC) or that of Sundberg (NaH in DMF, rt (**4a**) or 110 ^oC (**4b**)). The reductive alkylation, however, was successfully applied to furnish α-anilinoacetaldehyde acetals[6] (**6a**, **b**). Sulfonylation of **6a**, **b** with methanesulfonyl chloride failed but the acylation prodeeded smoothly with TFAA to yield trifluoroacetanilides (**7a**, **b**) in good yields. In effecting the ring closure, Sundberg conditions were superior compared to that of Nordlander: while the former gave pure trifluoracetylindole (**8b**) over 50% after recrystallisation, the yield of the latter did not exceeded 25% and the product needed chromatographic purification. Although the indolisation of **7a** furnished **8a**, the loss of *i*-Pr group of the

Scheme 2



sulfonic ester occurred during the ring closure and neither the free sulfonic acid nor its salts could be isolated from the hydrolysed reaction mixture. The introduction of the (1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-substituent at the 3 position of the indole is effected by methanolic KOH and *N*-methyl-4-piperidone. The trifluoroacetyl indole (**8b**) can either directly be applied in this reaction or hydrolysed by KOH-EtOH at rt previously to indole (**9**). The yield of the two-step procedure is about 15% higher than that of the one-step procedure.

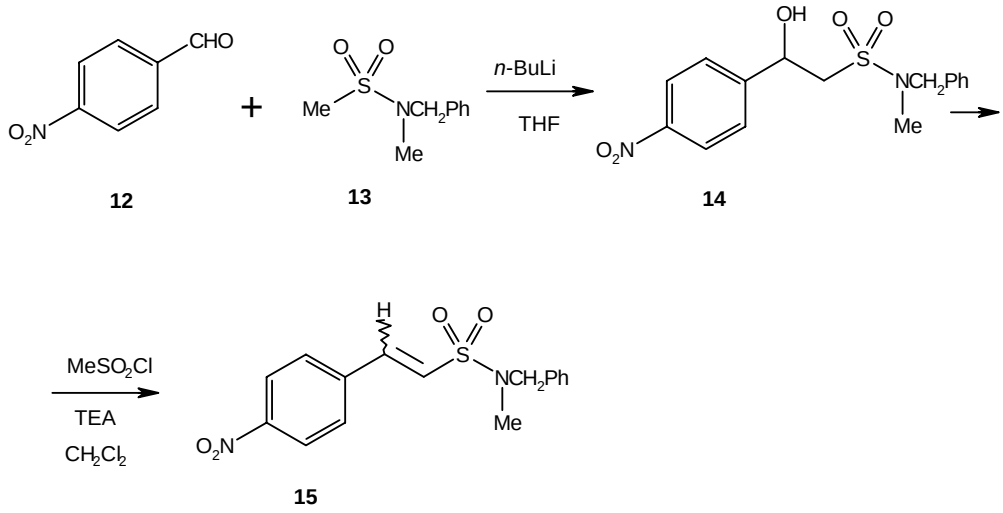
The reported condensation of *N*-methyl-1*H*-indole-5-ethanesulfonamide and *N*-methyl-4-piperidone gave the 3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)indole in 30% yield.[3a] The replacement of the sulfonamide

N-H to *N*-benzyl in this reaction improved the yield considerably as **9** furnished **10** in 85% yield. We envisaged the hydrogenation of the exocyclic double bond and the hydrogenolysis of the *N*-benzyl group as a one-pot reaction by catalytic hydrogenation. While the reduction of the exocyclic double-bond was very facile, the forcing-conditions (5 bar, 50-60 ^{o}C) necessary to remove an amide-benzyl group resulted in the hydrogenation of the endocyclic double bond at the indole-2,3 position without the hydrogenolysis of the benzyl group. The deprotection of the sulfonamide-*N* atom, finally carried out by dissolving-metal reduction of the sulfonamide (**11**), completed the synthesis of Naratriptan in 16% overall yield. from **3b**.

Synthesis of vinyl sulfonic acid derivatives

Screening the literature for a practical, low-cost procedure to prepare 2-(4-nitrophenyl)ethene-sulfonamides as precursors for **3b** revealed that base-mediated condensation of 4-nitrobenzaldehyde and methanesulfonamides offers a facile way for these compounds. The Knoevenagel-type condensation[7] of phenylaminosulfonylacetic acid with 4-nitrobenzaldehyde has been effected by piperidinium acetate in refluxing toluene but the product contains methanesulfonanilide owing to the concomitant decarboxylation. The one-pot synthesis of vinylsulfonamides[8] through the addition of *N*-Boc-*N*-alkyl-methanesulfonamides on 4-nitrobenzaldehyde followed by elimination in the presence of *t*-BuOK seemed attractive. In our case, however, the reaction of *N*-Boc-*N*-methyl-methanesulfonamide with 4-nitrobenzaldehyde in THF at -78 ^{o}C with *t*-BuOK resulted in the formation of several major components which failed to give a single elimination product so this reaction was not further investigated. While *N*-benzyl-*N*-methylmethanesulfonamide (**13**) and 4-nitrobenzaldehyde failed to react under the same conditions, a smooth addition occured to give the hydroxysulfonamide (**14**) when using *n*-BuLi instead of *t*-BuOK (Scheme 3). The elimination proceeded quantitatively in the presence of mesyl chloride and triethylamine to give **15**. As none of these processes seemed satisfactory from industrial point of view, we decided to prepare the vinylsulfonamides by the classical method from amines and sulfonylchlorides. We have developed a facile synthesis of 2- (4-nitrophenyl)ethenesulfonic acid (**19**), the immediate precursor of 2-(4-aminophenyl)ethanesulfonic acid (**23**), in which the yields are almost quantitative and none of the products needs purification (Scheme 4). This acid (**19**) have been prepared by the nitration[9] of 2-phenyl-1-ethenesulfonic acid, by the sulfonylation of 4-nitrostyrene with SO_3,[10] and in the Wittig-Horner reaction of triethyl α-phosphorylmethanesulfonate[11] and 4-nitrobenzaldehyde with *n*-BuLi. The ethyl ester of **19** is formed in the latter case, NaI is used to dealkylate the ester. Alkyl mesylates undergo α-deprotonation easier than mesyl amides, and isopropyl[12] and isobutyl methanesulfonates[13] are reported to form stable α-carbanions capable of undergoing alkylation with alkyl iodides or even adding on formyl group.[14] Surprisingly, however, the alkyl mesylates have seldom been applied for the preparation of

Scheme 3



vinylsulfonates[15] yet The carbanion derived from isopropyl mesylate was used to prepare the acid (**19**) in our procedure according to Scheme 4. The sulfonyl chloride (**20**) was prepared in good yield from the acid (**19**). The sulfonylation of methylamine, however, was accompanied by addition of the amine on the double bond and the ratio of the two product (**21**, **22**) could not be affected by altering the reaction conditions indicating that the vinylsulfonamide and the vinylsulfonyl chloride have similar reactivity in conjugate addition. The Michael-type addition of vinyl sulfonamides is well-documented.[11] When *N*-methyl-*N*-benzylamine was sulfonylated, no nucleophilic addition occurred probably because of steric reasons, and the sulfonamide (**15**) was formed exclusively. Catalytic reduction of the nitro group and the double bond can be accomplished simultaneously yielding the aniline (**3a, b**). It is worth mentioning that dioxane is the solvent of choice for this reduction while other solvents, either protic or aprotic, decrease the yield considerably in case of **3b** or gave no aniline at all as in case of **3a**.

ACKNOWLEDGEMENT

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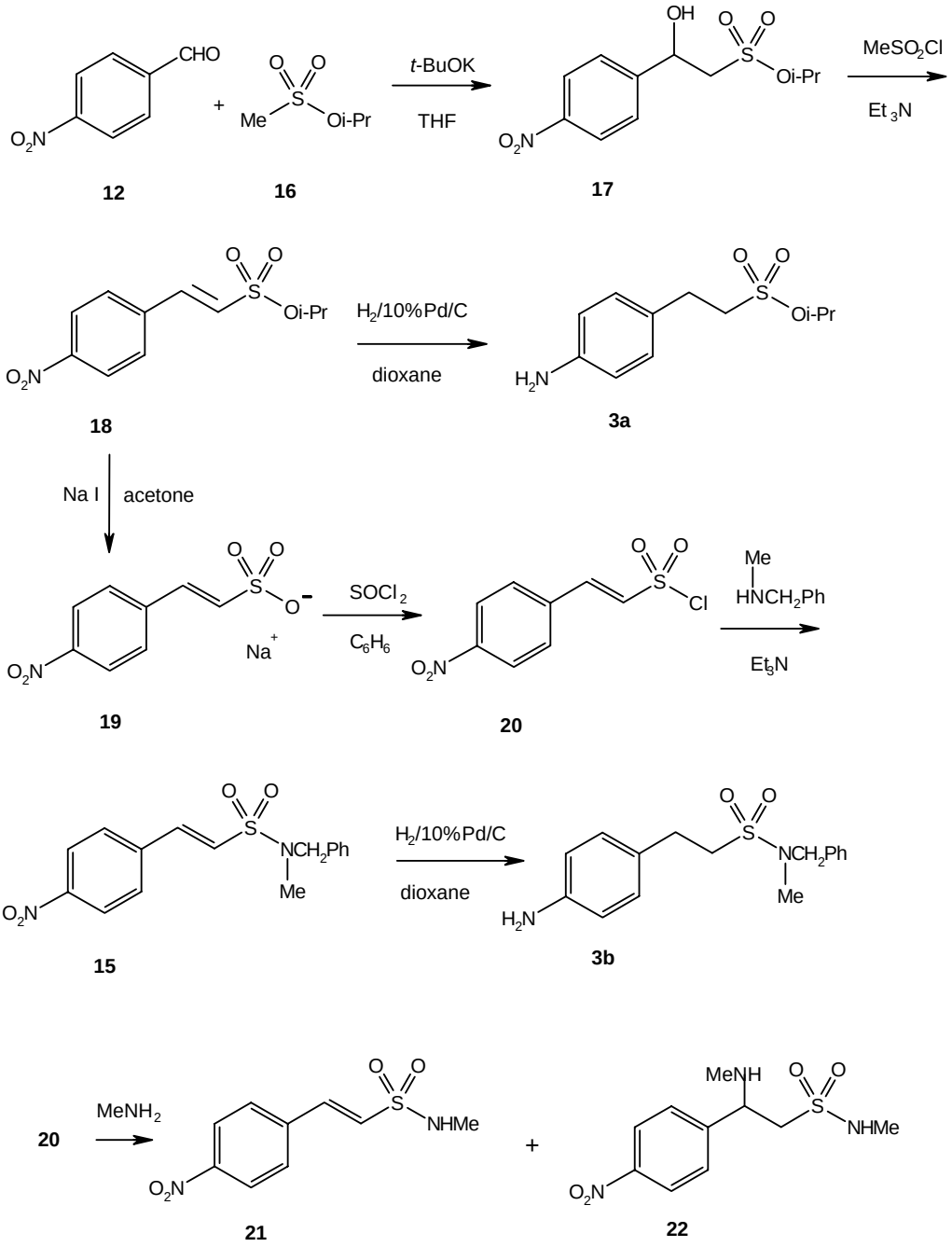
EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded at 250 MHz or 62.5 MHz, respectively, on a Bruker AC 250 spectrometer. All δ values are given in ppm, TMS was used as an internal standard. HRMS spectra were measured on a VG ZAB-2SEQ instrument (direct inlet at 200 ^{o}C, EI). Column chromatography was performed on Merck silica gel (0.63-0.20 mm). IR spectra were measured on Perkin-Elmer 1600 series FTIR spectrophotometer. All chemicals were reagent grade and used without further purification. *N*-

Methyl-*N*-benzylamine[16] (**13**) and isopropyl methanesulfonate[17] (**16**) were prepared by standard procedures.

Scheme 4



2-(4-Aminophenyl)ethanesulfonic acid isopropyl ester (**3a**).

2-(4-Nitrophenyl)ethenesulfonic acid isopropyl ester (**18**) (10 g, 36.9 mmol) was hydrogenated in dioxane (170 mL) with 10% Pd/C (1 g) at rt and 1 bar for 24 h. The reaction mixture was filtered, the dioxane

solution was rotary evaporated while keeping the bath temperature under 25 °C to give 7.2 g (80 %) of **3a** as a colorless oil. The product slowly polimerizes at rt but stable at -20 °C for weeks. ^{1}H NMR ($CDCl_3$) δ: 1.40 (d, 6H, *J*=6.5 Hz), 3.00 (m, 2H), 3.25 (m, 2H), 3.55 (br s, 2H), 4.92 (m, 1H, *J*=6.5 Hz), 6.62 (d, 2H, *J*=8.5 Hz), 6.95 (d, 2H, *J*=8.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 23.11; 28.96; 52.93; 76.72; 115.4; 126.91; 129.20, 145.60. Analysis was carried out on the *N*,*N*-dimesylate: Anal. Calcd for $C_{13}H_{21}NO_7S_3$: C, 39.08; H, 5.30; N, 3.51; S, 24.08. Found: C, 38.49; H, 5.48; N, 3.41; S, 23.86. IR of dimesylate (KBr): 1361, 1160, 911 cm^{-1}.

2-(4-Aminophenyl)ethanesulfonic acid benzylmethylamide (**3b**)

2-(4-Nitrophenyl)ethenesulfonic acid benzylmethylamide (**15**) (10 g, 0.301 mol) was hydrogenated in dioxane (170 mL) with 10% Pd/C (1 g) at rt and 1 bar for 24 h. The reaction mixture was filtered, the dioxane solution was rotary evaporated to give 8 g (88 %) of **3b** as yellow crystals, mp 85-87 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$) δ: 2.75 (s, 3H), 2.95-3.08 (m, 2H), 3.12-3.22 (m, 2H), 3.64 (br s, 2H), 4.33 (s, 2H), 6.62 (d, 2H, *J*=8.6 Hz), 6.98 (d, 2H, *J*=8.6 Hz), 7.35 (s, 5H). ^{13}C NMR ($CDCl_3$) δ: 28.66; 34.25; 52.10; 53.80; 115.44; 127.75; 127.98; 128.29; 128.73; 129.21; 135.87; 145.23. IR (KBr): 3462, 3426, 3372, 3352, 1337, 1151 cm^{-1}. Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20; S, 10.53. Found: C, 62.84; H, 6.48; N, 9.10; S, 10. 36.

2-(4-Methanesulfonylaminophenyl)ethanesulfonic acid isopropyl ester (**4a**)

To the stirring solution of 2-(4-aminophenyl)ethanesulfonic acid isopropyl ester (**3a**) (3.70 g, 15.2 mmol) in CH_2Cl_2 (100 mL) and pyridine (5.2 mL, 65 mmol) was added dropwise methanesulfonyl chloride (1.75 mL, 21.8 mmol) in CH_2Cl_2 (70 mL) at 3 °C over a period of 1 h. The reaction mixture was stirred at 3 °C for an additional 3 h then poured onto ice (200 g). The organic phase was separated, washed with water (2x50 mL), dried ($MgSO_4$), and evaporated in vacuum to give 3.13 g (64%) of **4a** as an oil which was sufficiently pure for spectral analysis. ^{1}H NMR ($CDCl_3$) δ: 1.40 (d, 6H, *J*=6.3 Hz), 2.95 (s, 3H), 3.10 (m, 2H), 3.30 (m, 2H), 4.96 (m, 1H, *J*=6.3 Hz), 7.20 (s, 4H). IR (film): 3182, 1352, 1155 cm^{-1}.

2-(4-Methanesulfonylaminophenyl)ethanesulfonic acid benzylmethylamide (**4b**)

To the stirring solution of 2-(4-aminophenyl)ethanesulfonic acid benzylmethylamide (**3b**) (3.04 g, 10 mmol) in CH_2Cl_2 (100 mL) and pyridine (2.6 mL, 33 mmol) was added dropwise methanesulfonyl chloride (1 mL, 13 mmol) in CH_2Cl_2 (30 mL) at 3 °C over a period of 1 h. The reaction mixture was stirred at 3 °C for an additional 3 h then poured onto ice (200 g). The organic phase was separated, washed with water (2x50 mL) then evaporated in vacuum to give 2.07 g (54%) of **4b**, mp 71-73 °C (ethanol). ^{1}H NMR

($CDCl_3$) δ: 2.78 (s, 3H), 2.93 (s, 3H), 3.12 (m, 2H), 3.19 (m, 2H), 4.32 (s, 2H), 7.18 (d, 2H, *J*=7.5 Hz), 7.37 (m, 7H). IR (KBr): 3212, 1348, 1153 cm^{-1}. Anal. Calcd for $C_{17}H_{22}N_2O_4S_2$: C, 53.38; H, 5.80; N, 7.32; S, 16.77. Found: C, 53.20; H, 5.91; N, 7.22; S, 16. 42.

2-[4-(2,2-Dimethoxyethylamino)phenyl]ethanesulfonic acid isopropyl ester (**6a**).

To the mixture of 2-(4-aminophenyl)ethanesulfonic acid isopropyl ester (**3a**) (3.0 g, 12.3 mmol) and 10% Pd/C (0.4 g) in ethanol (100 mL) was added a solution of dimethoxyacetaldehyde (3.3 mL, 21.8 mmol, 60% in H_2O) and the whole was stirred under hydrogen atmosphere at rt for 8 h. The catalyst was filtered off, the ethanolic solution was rotary evaporated and the oily residue was purified by flash-cromatography with hexane:ethyl acetate (4:1) to give 2.9 g (71%) of **6a**, as colorless oil. ^1H NMR ($CDCl_3$) δ: 1.40 (d, 6H, *J*=6.3 Hz), 3.03 (m, 2H), 3.25 (m, 2H), 3.3-3.55 (m, 2H), 3.45 (s, 6H), 4.56 (t, 1H, *J*=5.7 Hz), 4.98 (m, 1H, *J*=6.3 Hz), 6.58 (d, 2H, *J*=8 Hz), 7.03 (d, 2H, *J*=8 Hz). ^{13}C NMR ($CDCl_3$) δ: 23.00 ; 28.87; 45.38; 52.77; 53.72; 76.47; 102.48; 113.20; 126.07; 129.14; 146.96. IR (film): 3391, 1336, 1142 cm^{-1}. HRMS (M^+) calcd for $C_{15}H_{25}NO_5S$ 331.1453; found: 331.1448.

2-[4-(2,2-Dimethoxyethylamino)phenyl]ethanesulfonic acid benzylmethylamide (**6b**)

To the mixture of 2-(4-aminophenyl)ethanesulfonic acid benzylmethylamide (**3b**) (8.0 g, 26.3 mmol) and 10% Pd/C (1.4 g) in ethanol (200 mL) was added a solution of dimethoxyacetaldehyde (6.7 mL, 44.4 mmol, 60% in H_2O) and the whole was stirred under hydrogen atmosphere at rt for 8 h. The catalyst was filtered off, the ethanolic solution was rotary evaporated and the crystalline residue was washed with isopropanol to give 8.6 g (84%) of **6b**, mp 65-67 ^oC (ethyl acetate). ^1H NMR ($CDCl_3$) δ: 2.72 (s, 3H), 2.96-3.05 (m, 2H), 3.12-3.20 (m, 2H), 3.22 (d, 2H, *J*=5.5 Hz), 3.40 (s, 6H), 4.32 (s, 2H), 4.56 (t, 1H, *J*=5.5 Hz), 6.58 (d, 2H, *J*=8.3 Hz), 7.00 (d, 2H, *J*=8.3 Hz), 7.33 (s, 5H). ^{13}C NMR ($CDCl_3$) δ: 28.58; 34.22; 45.41; 52.07; 53.77; 53.86; 102.48; 113.33; 126.82; 127.93; 128.26; 128.69; 129.18; 135.87; 146.79. IR (KBr): 3408, 1524, 1332, 1144, 1063 cm^{-1}. Anal. Calcd for $C_{20}H_{28}N_2O_4S$: C, 61.20; H, 7.19; N, 7.14; S, 8.17. Found: C, 61.25; H, 7.18; N, 7.09; S, 8.06.

2-{4-[(2,2-Dimethoxyethyl)-(2,2,2-trifluoroacetyl)amino]phenyl}ethanesulfonic acid isopropyl ester **(7a**)

To the solution of 2-[4-(2,2-dimethoxyethylamino)phenyl]ethanesulfonic acid isopropyl ester **(6a**) (9.0 g, 27.3 mmol) and triethylamine (4.5 mL, 32 mmol) in dry toluene (120 mL) was added TFAA (4.23 mL, 30 mmol) over a period of 15 min at 0 ^oC. The reaction mixture was kept at rt for 16 h, then cooled again to 0 ^oC and triethylamine (4.0 mL, 29 mmol) and TFAA (3.0 mL, 21.3 mmol) were added as before. After 16

h at rt, the solution was rotary evaporated, the oily residue dissolved in CH_2Cl_2 (100 mL) and washed with cold H_2O (3x50 mL). The CH_2Cl_2 solution was dried ($MgSO_4$), and rotary evaporated to give an oil (10 g) which was purified by flash-cromatography with hexane:ethyl acetate (5:1) to give 8.0 g (69%) of **7a** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 1.40 (d, 6H, *J*=6.8 Hz), 3.1-3.25 (m, 2H), 3.25-3.40 (m, 2H), 3.30 (s, 6H), 3.78 (d, 2H, *J*=5.4 Hz), 4.60 (t, 1H, *J*=5.4 Hz), 4.98 (m, 1H, *J*=6.8 Hz), 7,22 (s, 4H). IR (film): 1708, 1201, 1148 cm^{-1}. HRMS (M^+) calcd for $C_{17}H_{24}NO_6F_3S$ 427.1277; found: 427.1273.

N-{4-[2-(Benzylmethylsulfamoyl)ethyl]phenyl}-N-(2,2-dimethoxyethyl)-2,2,2-trifluoroacetamide **(7b)**

To the solution of 2-[4-(2,2-dimethoxyethylamino)phenyl]ethanesulfonic acid benzylmethylamide **(6b)** (20.0 g, 51 mmol) and triethylamine (38.0 mL, 271 mol) in dry CH_2Cl_2 (600 mL) was added TFAA (37.0 mL, 262 mmol) in dry CH_2Cl_2 (60 mL) over a period of 3 h at 0 °C. The reaction mixture was kept at rt for 16 h, then poured onto ice (200 g) and stirred for 1 h. The organic phase was separated, washed with H_2O (3x100 mL) and dried ($MgSO_4$). The dry solution was rotary evaporated and the oily residue (25 g) was purified by flash-cromatography with hexane:ethyl acetate (5:1) to give 21.6 g (87%) of pure **7b** as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 2.75 (s, 3H), 3.1-3.30 (m, 4H), 3.33 (s, 6H), 3.70 (d, 2H, *J*=5.6 Hz), 4.33 (s, 2H), 4.63 (t, 1H, *J*=5.6 Hz), 7,24 (s, 5H), 7.35 (s, 4H). ^{13}C NMR ($CDCl_3$) δ: 29.07; 34.24; 51.31; 52.60; 53.75; 53.76; 100.31; 116.24 (q, *J*=287 Hz); 128.05; 128.28; 128.76; 128.83; 129.21; 135.67; 138.25; 139.26; 157.28 (q, *J*=7.5 Hz). IR (film): 1698, 1332, 1205, 1153 cm^{-1}. HRMS (M^+) calcd for $C_{22}H_{27}N_2O_5F_3S$ 488.1593; found: 488.1597.

2-(1H-Indol-5-yl)ethanesulfonic acid (**8a**)

To dry chlorobenzene (50 mL), well stirred and kept at 115-120 °C, were added 2-{4-[(2,2-dimethoxyethyl)-(2,2,2-trifluoroacetyl)amino]phenyl}ethanesulfonic acid isopropyl ester (**7a**) (0.8 g, 1.87 mmol) in chlorobenzene (8 mL) and $TiCl_4$ (0.6 mL, 5.5 mmol) in chlorobenzene (4 mL) simultaneously over a period of 10 min. The reaction mixture was stirred at 125-130 °C for additional 25 min then cooled fast to rt with icy water and poured into the mixture of ice (25 g) and $NaHCO_3$ (6 g). The aqueous phase was separated, evaporated to dryeness and extracted with MeOH (2x40 mL). Evaporation of MeOH gave 2.2 g brown solid the ^{1}H NMR spectrum of which showed that of **8a**. Attempts to separate **8a** from inorganic materials were unsuccessful. ^{1}H NMR (D_2O) δ : 3.15-3.65 (m, 4H), 6.55 (d, 1H, *J*=3 Hz), 7.21 (d, 1H, *J*=8.7 Hz), 7,40 (d, 1H, *J*=3 Hz), 7.52 (d, 1H, *J*=8.7 Hz), 7.60 (s, 1H).

2-[1-(2,2,2-Trifluoroacetyl)-1H-indol-5-yl]ethanesulfonic acid benzylmethylamide (**8b**)

To dry chlorobenzene (150 mL), well stirred and kept at 100-105 °C, were added *N*-{4-[2-(benzylmethylsulfamoyl)ethyl]phenyl}-*N*-(2,2-dimethoxyethyl)-2,2,2-trifluoroacetamide (**7b**) (14 g, 28.6

mmol) in chlorobenzene (105 mL) and $TiCl_4$ (8.4 mL, 76.6 mmol) in chlorobenzene (55 mL) simultaneously over a period of 8 min. The reaction mixture was stirred at 105-110 ^oC for additional 9 min then cooled fast to 60 ^oC with icy water and poured onto the mixture of ice (150 g) and $NaHCO_3$ (60 g). The organic phase was separated, the aqueous phase extracted with CH_2Cl_2 (2x60 mL), and the combined organic phases dried ($MgSO_4$). The solvents were evaporated (high vacuum) to give a brown crystalline mass recrystallised from CH_2Cl_2 to give 6.2 g (51%) of pure **8b**, mp 106-110 ^oC. ^1H NMR: ($CDCl_3$) δ: 2.78 (s, 3H), 3.25 (s, 4H), 4.35 (s, 2H), 6.73 (d, 1H, *J*=4 Hz), 7.25 (m, 1H), 7.32 (s, 5H), 7.43 (s, 1H), 7.51 (m, 1H), 8.38 (d,1H, *J*=8.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 29.48; 34.32; 52.00; 53.83; 112.27; 119.20 (q, *J*=274 Hz); 117.13; 121.06; 124.52; 124.59; 126.44; 128.06; 128.30; 128.46; 130.89; 134.73; 135.70, 153.00 (q, *J*=8.5 Hz). IR (KBr): 1723, 1166, 1147 cm^{-1}. Anal. Calcd for $C_{20}H_{19}N_2O_3F_3S$: C, 56.60; H, 4.51; N, 6.60; S, 7.55. Found: C, 56.44; H, 4.37; N, 6.65; S, 7.43.

2-(1H-Indol-5-yl)ethanesulfonic acid benzylmethylamide (**9**)

To the solution of KOH (4.0g, 71 mmol) in MeOH (200 mL) was added 2-[1-(2,2,2-trifluoroacetyl)-1*H*-indol-5-yl]ethanesulfonic acid benzylmethylamide (**8b**) (4.5 g, 10.6 mmol) at rt. After standing for 2 h the pH was adjusted to 7 (10% aq. HCl solution), the inorganic salt separated was filtered off, and the filtrate was evaporated to dryeness. The product was extracted with CH_2Cl_2 (80 mL) and isolated by evaporation of the solvent to give 2.9 g (84%) of **9**, mp 70-72 ^oC (ethyl acetate). ^1H NMR: ($CDCl_3$) δ: 2.78 (s, 3H), 3.25 (m, 4H), 4.33 (s, 2H), 6.51 (s, 1H), 7.02 (d, 1H, *J*=8.3 Hz), 7.21 (m, 1H), 7.38 (s, 6H), 7.49 (s, 1H), 8.22 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 29.00; 34.31; 51.57; 53.82; 120.94; 127.95; 128.08; 128.31; 128.78; 129.19; 129.34; 129.53; 133.50, 135.71, 136.36. IR (KBr): 3320, 1732, 1329, 1145 cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_2O_2S$: C, 65.83; H, 6.14; N, 8.53; S, 9.76. Found: C, 65.76; H, 6.12; N, 8.37; S, 9.66.

2-[3-(1-Methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-5-yl]ethanesulfonic acid benzylmethylamide **(10)**

To the solution of 2-(1*H*-indol-5-yl)ethanesulfonic acid benzylmethylamide (**9**) (2.0 g, 6.09 mmol) in MeOH (70 mL) was added KOH (6.7 g, 120 mmol) followed by *N*-methyl-4-piperidone (2.3 mL, 19.7 mmol). The reaction mixture was refluxed under argon for 8 h, then cooled to 0 ^oC. After standing for a few hours at 0 ^oC, the product was filtered, washed with cold MeOH to give 2.13 (83%) of pure **10**, mp 188-190 ^oC (ethanol). ^1H NMR: ($CDCl_3$) δ: 1.65 (s, 2H), 2.43 (s, 3H), 2.60 (m, 1H), 2.70 (m, 1H), 2.78 (s, 3H), 3.19 (m, 2H); 3.24 (m, 4H), 4.33 (s, 2H), 6.15 (s, 1H), 7.02 (d, 1H, *J*=8.8 Hz), 7.14 (s, 1H), 7.35 (m, 6H), 7.71 (s, 1H), 8.23 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 28.54; 29.79; 34.16; 45.44; 52.09; 52.61; 53.74; 54.57; 111.85; 116.71; 117.84; 119.88; 122.28; 122.42; 125.33; 127.92; 128.19; 128.66; 129.09;

129.54; 135.74; 135.89. IR (KBr): 1338, 1147 cm^{-1}. Anal. Calcd for $C_{24}H_{29}N_3O_2S$: C, 68.05, H, 6.90, N, 9.92, S, 7.57. Found: C, 67.96; H, 6.82; N, 9.73; S, 7.51.

2-[3-(1-Methylpiperidin-4-yl)-1H-indol-5-yl]ethanesulfonic acid benzylmethylamide **(11)**

2-[3-(1-Methyl-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indol-5-yl]ethanesulfonic acid benzylmethylamide **(10)** (0.635 g, 1.5 mmol) was hydrogenated in MeOH (15 mL) with 10% Pd/C (0.13 g) at rt and 5 bar for 6 h. The reaction mixture was filtered and the catalyst washed with CH_2Cl_2 (10 mL).The combined solutions were rotary evaporated to give 0.54 g (85 %) of **11** as a white powder, mp 66-67 ^oC (ethanol). ^1H NMR: ($CDCl_3$) δ: 1.92 (m, 2H); 2.05 (d, 2H, *J*=9.3 Hz); 2.24 (t, 2H, *J*=10.9 Hz); 2.40 (s, 3H); 2.78 (s, 3H); 2.78 (m, 1H); 3.06 (d, 2H, *J*=9.8 Hz); 3.26 (d, 4H, *J*=11.4 Hz); 4.33 (s, 2H); 6.96 (m, 2H); 7.34 (m, 6H); 7.44 (s, 1H); 8.73 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 29.70; 32.58; 34.21; 46.10; 52.66; 53.74; 56.08; 111.66; 118.38; 120.39; 120.65; 122.15; 126.85; 127.85; 128.17; 128.37; 128.62; 135.41; 135.83. IR (KBr): 3397, 1332, 1150 cm^{-1}. Anal. Calcd for $C_{24}H_{31}N_3O_2S$: C, 67.73; H, 7.34; N, 9.87; S 7.53. Found: C, 67.35; H, 7.24; N, 9.61; S, 7.42.

2-[3-(1-Methylpiperidin-4-yl)-1H-indol-5-yl]ethanesulfonic acid methylamide (**2**, ***Naratriptan***)

To the stirring solution of 2-[3-(1-methylpiperidin-4-yl)-1*H*-indol-5-yl]ethanesulfonic acid benzylmethylamide (**11**) (0.426 g, 1 mmol) in liquid NH_3 (50 mL) and THF (9 mL) was added sodium (0.14 g, 6.1 mmol) at -78 ^oC over a period of 15 min and stirred for additional 0.5 h. Aqueous NH_4Cl (3 g, in 10 mL of H_2O) was added at -78 ^oC and the reaction mixture was allowed to reach rt. The aqueous phase was extracted with CH_2Cl_2 (3x15 mL) the combined organic phases were dried and evaporated to give a solid which, when treated with ethyl acetate, yielded 0.27 g (80%) of **2**, indentical with naratriptan[3] in all respect.

2-Hydroxy-2-(4-nitrophenyl)ethanesulfonic acid benzylmethylamide **(14)**

To the solution of *N*-benzyl-*N*-methylmethanesulfonamide (**13**, 1.7 g, 8.5 mmol) in dry THF (60 mL) was added *n*-BuLi solution (7.0 mL, 11.6 mmol, 1.6 M in hexanes) at -78 ^oC and the reaction mixture was stirred at this temperature for 0.5 h. 4-Nitrobenzaldehyde (1.4 g, 9.3 mmol) was added to the solution over a period of 2-3 min and stirred for an additional 4 h at -78 ^oC. The reaction mixture, while kept at the same temperature, was poured into aqueous NH_4Cl solution (5 g in 30 mL of H_2O). The dark-red mixture was allowed to warm to rt, the organic phase was separated, and the aqueous phase was extracted with $CHCl_3$ (30 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to give a red oil (3.0 g, 100%) which slowly crystallises, mp 73-75 ^oC (hexane-ethyl acetate). ^1H NMR ($CDCl_3$) δ: 2.84 (s, 3 H), 3.18 (m, 2H), 3.84 (d, 1H, *J*=2 Hz); 4.38 (s, 2H); 5.43 (m, 1H), 7.35 (s, 5H), 7.56 (d, 2H, *J*=8.7 Hz), 8.22

(d, 2H, *J*=8.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 34.32; 53.85; 57.70; 68.20; 123.94; 126.63; 128.26; 128.34; 128.87; 135.22; 147.62; 148.26. IR (KBr): 3464, 1520, 1349, 1147 cm^{-1}. Anal. Calcd for $C_{16}H_{18}N_2O_5S$: C, 54.85; H, 5.18; N, 7.99; S, 9.15. Found: C, 54.78; H, 5.22; N, 7.99; S, 9.06.

2-(4-Nitrophenyl)ethenesulfonic acid benzylmethylamide (**15**).

a.) To the solution of 2-hydroxy-2-(4-nitrophenyl)ethanesulfonic acid benzylmethylamide (**14**) (3.0 g, 8.5 mmol) in CH_2Cl_2 (30 mL)) was added triethylamine (1.5 mL, 10.7 mmol) at 0 ^{o}C in one portion followed by methanesulfonyl chloride (0.84 mL, 10.5 mmol) in CH_2Cl_2 (6 mL) over a period of 10 min at 0 ^{o}C. The reaction mixture was kept at 5 ^{o}C for 24 h then rotary evaporated to dryeness. The oily residue was dissolved in CH_2Cl_2 (30 mL) and stirred with 10% aqueous K_2CO_3 solution (10 mL) for 15 min. The organic layer was separated and evaporated to dryeness to give 2.4 g (85%) of **15,** mp 120-122 ^{o}C (ethanol). ^{1}H NMR ($CDCl_3$) δ: 2.78 (s, 3H), 4.32 (s, 2H), 6.79 (d, 1H, *J*=15.2 Hz), 7.32 (s, 5H), 7.49 (d, 1H, *J*=15.2 Hz), 6.60 (d, 2H, *J*=8.7 Hz), 8.23 (d, 2H, *J*=8.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 34.31; 53.92; 124.29; 127.07; 128.17; 128.45; 128.79; 128.89; 135.38; 138.76; 139.20; 148.70. IR (KBr):1518, 1350, 1146 cm^{-1}. Anal. Calcd for $C_{16}H_{16}N_2O_4S$: C, 57.82; H, 4.85; N, 8.43; S, 9.65. Found: C, 57.35; H, 4.86; N, 8.36; S, 9.52.

b.) To the suspension of 2-(4-nitrophenyl)ethenesulfonyl chloride (**20**) (4.8 g, 19.4 mmol) in benzene (40 mL)

was added the mixture of *N*-methyl-*N*-benzylamine (3 mL, 23.5 mmol) and triethylamine (4.2 mL, 30 mmol) at 0 ^{o}C over a period of 2 h. The reaction mixture was allowed to reach rt then stirred for additional 3 h. The precipitated material was filtered off, washed with H_2O to give 3.5 g (54%) of **15** identical with the compound described previously. Additional 1.70 g product can be obtained by evaporation of the benzene filtrate to dryeness and washing the solid residue with H_2O and cold MeOH. The combined yield is 80%.

2-Hydroxy-2-(4-nitrophenyl)ethanesulfonic acid isopropyl ester (**17**).

To the solution of *t*-BuOK (35 g, 312 mmol) in dry THF (650 mL) was added isopropyl methanesulfonate (**16**) (26 g, 188 mmol) at -78 ^{o}C in one portion and stirred for 0.5 h at -78 ^{o}C. 4-Nitrobenzaldehyde (26 g, 172 mmol) was added to the solution over a period of 2-3 min and stirred for an additional 4 h at -78 ^{o}C. The reaction mixture, while kept at the same temperature, was poured into aqueous NH_4Cl solution (120 g in 300 mL of H_2O). The dark-red mixture was warmed to rt, the organic phase separated and rotary evaporated to give an oil which was dissolved in $CHCl_3$ (300 mL), dried ($MgSO_4$) and evaporated to give a pale yellow oil which slowly crystallises to give 47 g (86%) of **17**, mp 49-51 ^{o}C (hexane-ethyl acetate).

^{1}H NMR ($CDCl_3$-DMSO-d_6) δ: 0.94 (d, 3 H, *J*=6 Hz), 1.10 (d, 3H, *J*=6 Hz), 3.00 (dd, 1 H, *J*=13.7 Hz, *J*=5.4 Hz), 3.22 (dd, 1 H, *J*=13.4 Hz, *J*=4.5 Hz), 3.48 (m, 1H, *J*=6 Hz), 4.92 (m, 1H), 7.52 (d, 2H, *J*=8.4 Hz), 8.06 (d, 2H, *J*=6 Hz). ^{13}C NMR ($CDCl_3$) δ: 21.17; 22.83; 58.59; 70.88; 74.73; 123.59; 127.51; 147.36; 149.89. IR (KBr): 3374, 1519, 1352, 1196 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_6S$: C, 45.67; H, 5.23; N, 4.84; S, 11.08. Found: C, 45.21; H, 5.48; N, 4.49; S, 10.70.

2-(4-Nitrophenyl)ethenesulfonic acid isopropyl ester (**18**).

To the 2-hydroxy-2-(4-nitrophenyl)ethanesulfonic acid isopropyl ester (**17**) (47.0 g, 162 mmol) in $CHCl_3$ (300 mL) was added triethylamine (29 mL, 207 mmol) during 15 min at 0 °C, followed by methanesulfonyl chloride (16.4 mL, 204 mmol) in $CHCl_3$ (60 mL) over a period of 1 h at 0 °C. The reaction mixture was kept at 5 °C for 24 h then poured onto ice (200 g). The organic phase was washed with H_2O (2x100 mL), then dried ($MgSO_4$) and rotary evaporated. The crystalline residue was washed with cold methanol to give 36.4 g (82%) of **18**, mp 68-70 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$) δ: 1.40 (d, 3H, *J*=6.3 Hz), *J*=6.3 Hz), 4.90 (m, 1H, *J*=6.3 Hz), 6.90 (d, 1H, *J*=16 Hz), 7.60 (d, 1H, *J*=16 Hz), 7.65 (d, 2H, *J*=8.5 Hz), 8.25 (d, 2H, *J*=8.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 22.80; 78.01; 124.15; 126.90; 129.10; 138.05; 140.08, 149.20. IR (KBr): 1520, 1343, 1171 cm^{-1}. Anal. Calcd for $C_{11}H_{13}NO_5S$: C, 48.70; H, 4.83; N, 5.16; S, 11.82. Found: C, 47.77; H, 4.88; N, 5.09; S, 11.60.

Sodium 2-(4-nitrophenyl)ethenesulfonate (**19**)

The solution of 2-(4-nitrophenyl)ethenesulfonic acid isopropyl ester (**18**), (19 g, 69 mmol) and NaI.2 H_2O (12.8 g, 69 mmol) in acetone (280 mL) was refluxed for 6 h, then allowed to cool to rt. The product precipitated was filtered off, and washed with acetone (20 mL) to give 16.6 g of raw **19** used without further purification. This raw material (1 g) was crystallised from saturated NaCl solution (3.5 mL) to give pure **19** (0.7 g) identical in all respect with the compound already described.[18] ^{1}H NMR (D_2O) δ: 7.04 (d, 1H, *J*=15.6 Hz), 7.21 (d, 1H, *J*=15.6 Hz), 7.55 (d, 2H, *J*=8 Hz), 8.07 (d, 2H, *J*=8 Hz).

2-(4-Nitrophenyl)ethenesulfonyl chloride (**20**)

To the suspension of sodium 2-(4-nitrophenyl)ethenesulfonate (**19**) (5.0 g, 19.7 mmol) in benzene (140 mL) containing dimethylformamide (0.1 mL) was added $SOCl_2$ (6 mL, 82 mmol) and the reaction mixture was refluxed for 5 h. The solution was evaporated and the crystalline residue (4.5 g) was recrystallised from diethyl ether to give **20** (3.1 g, 64%) being identical in all respect with the compound already described.[10]

2-(4-Nitrophenyl)ethenesulfonic acid methylamide (**21**) and ***2-Methylamino-2-(4-nitrophenyl)ethane-sulfonic acid methylamide*** (**22**)

To the stirring suspension of 2-(4-nitrophenyl)ethenesulfonyl chloride (**20**) (16.6 g, 67 mmol) in benzene (200 mL) cooled to 0 ^{o}C was added the solution of $MeNH_2$ (23.0 mL, 268 mmol, 36% in H_2O) at the same temperature over a period of 20 min. The reaction mixture was allowed to reach rt and stirred for 3 h. The reaction mixture was rotary evaporated to dryeness and the residue was washed with H_2O (2x100 mL) to give 13.4 g solid as a 1:1 mixture of **21** and **22** . Recrystallisation of the solid from $CHCl_3$ gave 3.2 g of pure **22**, and flash chromatography of the mother liquor furnished 1.6 g of pure **21,** mp 148-150 ^{o}C, ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ: 2.58 (d, 3H, *J*=4.9 Hz), 7.16 (q, 1H, *J*=4.9 Hz), 7.21 (d, 1H, *J*=15.6 Hz), 7.40 (d, 1H, *J*=15.6 Hz), 7.87 (d, 2H, *J*=8.8 Hz), 8.19 (d, 2H, *J*=8.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 28.06, 123.38, 128.86, 129.33, 136.20, 138.22, 148.70. IR (KBr): 3289, 1519, 1348, 1148 cm^{-1}. Anal. Calcd for $C_9H_{10}N_2O_4S$: C, 44.62; H, 4.16; N, 11.56; S, 13.24. Found: C, 44.76; H, 4.19; N, 11.54; S, 13.20. **22**: mp: 128-130 ^{o}C, ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ: 2.17 (s, 3H), 2.68 (s, 3H), 3.13 (dd, 1 H, *J*=14 Hz, *J*=3 Hz), 3.33 (dd, 1 H, *J*=14 Hz, *J*=10 Hz), 4.27 (dd, 1H, *J*=3 Hz, *J*=10 Hz), 7.56 (d, 2H, *J*=8 Hz), 8.27 (d, 2H, *J*=8 Hz). ^{13}C NMR ($CDCl_3$) δ: 28.78; 33.83; 56.47; 59.90; 124.07; 128.15; 147.56; 148.15. IR (KBr): 3307, 1521,1349, 1292. Anal. Calcd for $C_{10}H_{15}N_3O_4S$: C, 43.95; H, 5.53; N 15.37; S, 11.73. Found: C, 43.84; H, 5.53; N, 15.17; S, 11.53.

2-(4-Aminophenyl)ethanesulfonic acid (**23**)

The solution of sodium 2-(4-nitrophenyl)ethenesulfonate (**19**) (5 g, 19.9 mmol) and KOH (1.2 g, 21.4 mmol) in H_2O (150 mL) was hydrogenated with 10% Pd/C (0.6 g) at rt and 1 bar for 48 h. The reaction mixture was filtered, the solution rotary evaporated to 40 mL of volume and the pH adjusted to 3-4 (10% aq. HCl). The solid precipitate was filtered off and washed with H_2O (10 mL) to give 2.95 g (73.6%) of **23** as inner salt. ^{1}H NMR (D_2O) δ: 3.20 (m, 2H), 3.29 (m, 2H), 7.00 (d, 2H, *J*=8 Hz), 7.32 (d, 2H, *J*=8 Hz). ^{13}C NMR (D_2O) δ: 27.49, 50.63, 114.76, 127.30, 128.29, 142.28. IR (KBr): 3300, 1220, 1130 cm^{-1}. Anal. Calcd for $C_8H_{11}NO_3S$: C, 47.75; H, 5.51; N, 6.96; S, 15.93. Found: C, 47.21; H, 5.53; N, 6.65; S, 15.53.

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