3,4,8,9-Tetramethylene-*endo*-2,5:*endo*-7,10-dietheno-*cis*-decalin.[1] A New Exocyclic Diene Bridged Polycyclic Hydrocarbon[2]

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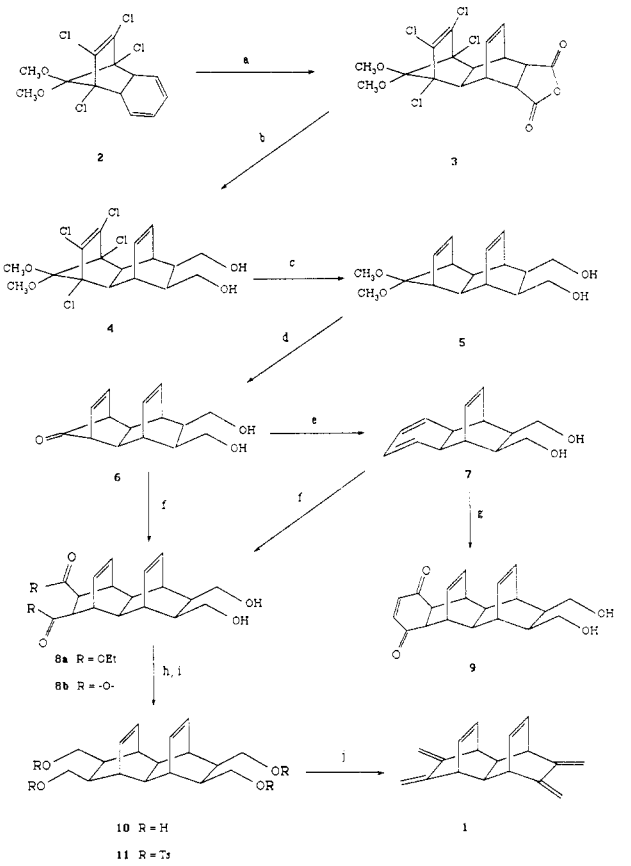
Carbocyclic molecules bridged by exocyclic diene units are theoretically and synthetically important. These molecules can be utilized as ligands for the preparation of metal complexes[3] and are attractive building blocks for the construction of bridged polycyclic systems via Diels–Alder cycloadditions with dienophiles.[4] Incorporation of additional unsaturation to the bridge of these molecules further modifies the chemical and spectroscopic properties of the exocyclic diene moiety[5] and hence provides suitable substrates for the investigation of proximity effects.[6] We now describe the synthesis and characterization of a new tetracyclic hexaene **1** that contains two exocyclic *s-cis*-butadiene moieties spatially separated by two parallel double bonds in a rigid C_{2v}-symmetric carbon framework.

The readily available Diels–Alder cycloadduct **3**[7] from the reaction of *endo*-1,8,9,10-tetrachloro-11,11-dimethoxytricyclo[6.2.1.$0^{2,7}$]undeca-3,5,9-triene (**2**)[8] and maleic anhydride was reduced by 2.0 equiv of lithium aluminum hydride ($LiAlH_4$) in dry tetrahydrofuran (THF) to furnish the corresponding diol **4** in 92% yield after flash chromatography on silica gel (CH_2Cl_2–hexane) (Scheme I). Dechlorination of **4** with Na–Bu^{t}OH in THF gave the diol **5** in 86% yield. The deprotection of the acetal functionality in **5** was effected with 20% H_2SO_4 in CH_2Cl_2 at 10 °C for 6 h to afford the keto diol **6** in 78% yield. Decarbonylation of **6** in boiling dimethoxyethane (DME) furnished the trienediol **7** in 82% yield. The trienediol **7** showed good stability and was shown to react with diethyl maleate, maleic anhydride, and *p*-benzoquinone to yield the respective Diels–Alder cycloadducts **8a** (92%), **8b** (83%), and **9** (84%). By heating **6** with diethyl maleate in toluene at 175 °C the cycloadduct **8a** could be directly obtained in 87% yield. Reduction of the diethoxycarbonyl moiety of **8a** or the carboxylic anhydride moiety of **8** with $LiAlH_4$ (3.5 equiv) furnished the symmetric tetrol **10** in 84% and 74% yield, respectively. A solution of **10** in pyridine was treated with toluenesulfonyl chloride to provide the corresponding tetratosylate **11** which, without further purification, was subsequently converted (Bu^{t}OK/DMSO)[9] to the title compound **1** in 43% yield after chromatography on silica gel (hexane). The diagnostic five types of hydrogen absorptions in the ^{1}H NMR spectrum and five-line ^{13}C NMR resonances at δ 147.4, 130.6, 102.4, 47.2, and 42.6 clearly illustrated its C_{2v} symmetry and fully established the structure of **1**.

Scheme I[a]



[a] (a) Maleic anhydride, benzene, 80 °C, 4 h; (b) $LiAlH_4$, THF, reflux, 3 h; (c) Na, *t*-BuOH, THF, reflux, 48 h; (d) 20% H_2SO_4, CH_2Cl_2, 10 °C, 6 h; (e) DME, reflux, 18 h; (f) diethyl maleate, toluene, 175 °C, 6 h (or maleic anhydride, DME, reflux, 18 h); (g) *p*-benzoquinone, DME, reflux, 18 h; (h) $LiAlH_4$, THF, 0 °C, 6 h and reflux, 1 h; (i) TsCl, py, 0 °C, 6 h; (j) *t*-BuOK, DMSO, 50 °C, 8 h.

Efforts are underway to study the physicochemical properties of **1**, and to explore the synthesis of interesting *syn-cis*-diethenodecalins using the intermediate **7** and the starting material **2**, which is, as demonstrated by this report, a useful synthetic equivalent of *cis*-9,10-dihydronaphthalene.

Experimental Section[10]

(1α,2β,3α,6α,7β,8α,11β,12β)-3,4,5,6-Tetrachloro-11,12-bis(hydroxymethyl)-13,13-dimethoxytetracyclo[6.2.2.1^{3,6}.0^{2,7}]trideca-4,9-diene (4). A solution containing 60.0 g (0.136 mol) of **3** in 500 mL of anhydrous THF was slowly added to an ice-cold suspension of 10.35 g (0.273 mol) of lithium aluminum hydride (LAH) in 300 mL of anhydrous THF. The mixture was stirred for 3 h at reflux temperature under a nitrogen atmosphere, and the reaction mixture was then cooled to 5 °C. The mixture was poured into a stirred, cold water–ether (200 mL/400 mL) mixture. The organic layer was separated, and the aqueous layer was extracted with ether (2 × 100 mL). The combined organic layer was washed with water (2 × 100 mL) and saturated aqueous sodium chloride (150 mL) and then dried over anhydrous magnesium sulfate. Filtration and concentration of the filtrate afforded crude **4**. This product was recrystallized from a 3:2 mixture of ether and hexane to give 53.00 g (92%) of pure **4**. The analytical sample was obtained by chromatography on a silica gel column

(1) (1α,2β,3α,6α,7β,8α)-4,5,9,10-Tetramethylenetetracyclo[6.2.2.2^{3,6}.0^{2,7}]tetradeca-11,13-diene.

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using ether–hexane (1:3) as eluent: mp 147–148 °C; $M^+ - Cl$ = 393.045 (calc 393.0429); ^1H NMR ($CDCl_3$) δ 2.23 (m, 2 H), 2.73 (m, 2 H), 2.77 (s, 2 H), 3.14 (s, 2 H, 2 OH), 3.49 (s, 3 H, OCH_3), 3.59 (s, 3 H, OCH_3), 3.52–3.58 (m, 4 H, 2 CH_2O), 5.94 (dd, 2 H, J = 4.0, 3.8 Hz); ^{13}C NMR ($CDCl_3$) δ 33.35 (d), 46.14 (d), 50.47 (d), 51.05 (q), 52.22 (q), 63.43 (t), 76.94 (s), 113.4 (s), 127.4 (s), 128.5 (d). Anal. Calcd for $C_{17}H_{20}Cl_4O_4$: C, 47.47; H, 4.68. Found: C, 47.28; H, 4.52.

(1α,2β,3α,6α,7β,8α,11β,12β)-11,12-Bis(hydroxymethyl)-13,13-dimethoxytetracyclo[6.2.2.1^{3,6}.0^{2,7}]trideca-4,9-diene (5). A solution of 50.0 g (0.116 mol) of **4** and 154 g (2.08 mol) of *tert*-butyl alcohol in dry THF (700 mL) was placed in a three-necked round-bottom flask containing a stirrer and an efficient condenser. Sodium (80.0 g, 3.48 mol) was added to this stirred solution in small pieces over a period of 45 min in a countercurrent of nitrogen. The mixture was vigorously stirred at reflux for 48 h, cooled to room temperature, and filtered to removed unreacted sodium. The filtrate was poured into ice–water (400 mL) and extrated with ether (2 × 300 mL). The combined ethereal layers were washed with brine (300 mL), dried, and concentrated. The resulting residue was recrystallized from a 2:1 mixture of ethyl acetate and hexane to afford 29.1 g (86%) of **5** as colorless crystals. The analytical sample was obtained by chromatography on a silica gel column using ethyl acetate–hexane (3:1) as eluent: mp 134–135 °C; M^+ = 292.1688 (calc 292.1675); ^1H NMR ($CDCl_3$) δ 2.21 (m, 2 H), 2.39 (s, 2 H), 2.46 (s, 2 H), 2.74 (m, 2 H), 2.76 (m, 2 H), 3.00 (s, 3 H, OCH_3), 3.15 (s, 3 H, OCH_3), 3.40–3.56 (m, 4 H, 2 OCH_2), 5.42 (dd, 2 H, J = 2.1, 1.8 Hz), 5.50 (dd, 2 H, J = 4.6, 3.0 Hz); ^{13}C NMR ($CDCl_3$) δ 37.65 (d), 39.77 (d), 48.28 (d), 48.99 (d), 49.64 (q), 51.89 (q), 64.41 (t), 120.3 (s), 130.5 (d), 131.2 (d). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.82; H, 8.34.

(1α,2β,3α,6α,7β,8α,11β,12β)-11,12-Bis(hydroxymethyl)tetracyclo[6.2.2.1^{3,6}.0^{2,7}]trideca-4,9-diene (6). A solution of 25.2 g (86.3 mmol) of **5** in methylene chloride (400 mL) with 20% sulfuric acid (100 mL) was stirred vigorously at 10 °C for 6 h. The organic layer was separated, and the aqueous layer was extracted with methylene chloride (2 × 100 mL). The combined organic layers were washed with water (3 × 100 mL), dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo to leave a residue, which was recrystallized from a 3:1 mixture of methylene chloride and hexane to afford 21.1 g (78%) of **6** as colorless crystals. The analytical sample was obtained by chromatography on a silica gel column using acetone–methylene chloride (1:19) as eluent: mp 133–134 °C; M^+ = 246.1277 (calc 246.1256); IR (KBr) 1772 cm^{-1} (C=O); ^1H NMR (pyridine-d_5) δ 2.44 (m, 2 H), 2.50 (s, 2 H), 2.89 (m, 2 H), 2.95 (m, 2 H), 3.57 (dd, 2 H, J = 10, 6.3 Hz), 3.89 (dd, 2 H, J = 10, 6.8 Hz), 5.66 (dd, 2 H, J = 4.5, 2.1 Hz), 5.81 (dd, 2 H, J = 2.4, 2.1 Hz), 6.09 (br, 2 OH, D_2O exch); ^{13}C NMR (pyridine-d_5) δ 36.56 (d), 37.69 (d), 48.10 (d), 52.28 (d), 62.29 (t), 128.8 (d), 132.3 (d), 200.0 (s). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.36. Found: C, 73.00; H, 7.55.

(1α,2β,7β,8α,11β,12β)-11,12-Bis(hydroxymethyl)tricyclo[6.2.2.0^{2,7}]dodeca-3,5,9-triene (7). A solution of 12.0 g (48.7 mmol) of **6** in 50 mL of dimethoxyethane (DME) was refluxed under nitrogen for 18 h until infrared spectral analysis of an aliquot indicated the lack of carbonyl absorption at 1772 cm^{-1}. Evaporation of the solvent under reduced pressure (25 °C) afforded a residue, which was then recrystallized from a 1:1 mixture of methylene chloride and hexane to provide 8.70 g (82%) of the trienediol **7**. An analytical sample was obtained by flash chromatography on a silica gel column with methylene chloride–hexane (1:10) as eluent: mp 169–170 °C; M^+ = 218.1297 (calc 218.1307); ^1H NMR ($CDCl_3$) δ 2.38 (m, 2 H), 2.47 (s, 2 H), 2.97 (s, 2 H), 3.17 (s, 2 H, 2 OH), 3.50–3.81 (m, 4 H, 2 OCH_2), 5.33 (m, 2 H), 5.45 (m, 2 H), 6.28 (dd, 2 H, J = 4.5, 3.3 Hz); ^{13}C NMR ($CDCl_3$) δ 40.40 (d), 45.71 (d, 2 peaks), 64.71 (t), 121.1 (d), 129.0 (d), 133.7 (d). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: 76.66; H, 8.28.

Diels–Alder Reactions of 7. A. Reaction with Diethyl Maleate. A solution of 1.20 g (5.50 mmol) of **7** and 1.14 g (6.63 mmol) of diethyl maleate in 10 mL of toluene was scaled in an autoclave and heated at 175 °C for 6 h. The solvent was removed under reduced pressure, and the white residue was chromatographed on a silica gel column with 2% of ethanol in methylene chloride as eluent to afford 1.98 g (92%) of the cycloadduct (1α,2β,3α,4β,5β,6α,7β,8α,9β,10β)-4,5-bis(ethoxycarbonyl)-9,10-bis(hydroxymethyl)tetracyclo[6.2.2.2^{3,6}.0^{2,7}]tetradeca-11,13-diene (**8a**). The analytical sample was recrystallized twice from a 1:1 mixture of methylene chloride and hexane: mp 155–156 °C; M^+ = 390.2043 (calc 390.2043); IR (KBr) 3254, 3036, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (t, 6 H, J = 7.2 Hz), 2.06 (s, 2 H), 2.18 (m, 2 H), 2.36 (br, 2 H), 2.76 (br, 2 H), 2.96 (s, 2 H), 3.41 (m, 2 H), 3.48 (m, 2 H), 3.75 (s, 2 H), 3.96 (m, 4 H), 5.65 (dd, 2 H, J = 3.3, 4.6 Hz), 5.79 (dd, 2 H, J = 3.3, 4.4 Hz); ^{13}C NMR ($CDCl_3$) δ 13.98 (q), 38.05 (d), 39.76 (d), 42.58 (d), 47.12 (d), 49.16 (d), 60.22 (t), 64.20 (t), 130.6 (d), 131.3 (d), 172.5 (s). Anal. Calcd for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.68; H, 7.70.

B. Reaction with Maleic Anhydride. A mixture of 1.24 g (5.69 mmol) of **7** and 0.69 g (7.04 mmol) of maleic anhydride in dry DME (20 mL) was refluxed for 18 h under a nitrogen atmosphere. The reaction mixture was cooled, and the crystallized, pure cycloadduct **8b** was collected by filtration. The filtrate was concentrated, and the residue remaining was chromatographed on silica gel using 2% of methanol in ethyl acetate as eluent to afford an additional crop of **8b**. The total yield was 1.37 g (76%). Recrystallization from DME–hexane (5:1) gave white crystals: mp 231–233 °C; M^+ = 316.1324 (calc 316.1311); IR (KBr), 1842, 1771 cm^{-1}; ^1H NMR (pyridine-d_5) δ 2.07 (s, 2 H), 2.44 (br, 2 H), 2.72 (br, 2 H), 3.01 (br, 2 H), 3.42 (s, 2 H), 3.60 (m, 2 H, 2 OCH), 3.94 (m, 2 H, 2 OCH), 5.69 (dd, 2 H, J = 3.9, 3.6 Hz), 5.78 (dd, 2 H, J = 3.9, 3.6 Hz), 6.04 (br, 2 H, 2 OH); ^{13}C NMR (pyridine-d_5) δ 37.67 (d), 38.75 (d), 41.39 (d), 46.90 (d), 47.54 (d), 62.35 (t), 131.84 (s, 2 peaks), 173.8 (s);

C. Reaction with *p*-Benzoquinone. Treatment of 0.42 g (1.93 mmol) of **7** with 0.29 g (2.68 mmol) of *p*-benzoquinone in DME as in the previous steps for the formation of **8b** gave 0.53 g (84%) of **9** as a light yellow crystalline product: mp 243–246 °C dec; M^+ = 326.1519 (calc 326.1537); IR (KBr) 1678 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 2.27 (br, 4 H), 2.48 (br, 2 H), 2.70 (br, 2 H), 2.99 (s, 2 H), 3.14 (br, 2 H), 3.50–3.58 (m, 4 H, 2 OCH_2), 5.68 (m, 2 H), 5.75 (m, 2 H), 6.61 (s, 2 H)

One-Pot Decarbonylation/Diels–Alder Reaction of 6 with Diethyl Maleate. A solution of 4.52 g (18.4 mmol) of **6** and 3.79 g (22.0 mmol) of diethyl maleate in toluene (30 mL) was sealed in an autoclave and heated at 175 °C for 8 h. The toluene was removed under reduced pressure, and the resulting residue was recrystallized from a 1:1 mixture of methylene chloride and hexane to afford 6.24 g (87%) of **8a**.

(1α,2β,3α,4β,5β,6α,7β,8α,9β,10β)-4,5,9,10-Tetrakis(hydroxymethyl)tetracyclo[6.2.2.2^{3,6}.0^{2,7}]tetradeca-11,13-diene (10). A solution of 5.45 g (14.0 mmol) of **8a** in LAH distilled THF (100 mL) was added dropwise to a stirred suspension of 1.86 g (49.0 mmol) of LAH in THF (50 mL) at 0 °C under a nitrogen atmosphere. After 6 h at 0 °C, the reaction mixture was refluxed for another 1 h. The excess LAH was destroyed by the careful addition of water (5 mL) and then 15 g of sodium bicarbonate. The white precipitate, which formed, was filtered and washed with warm ethanol (3 × 45 mL). The filtrate was passed through silica gel with ethanol to remove inorganic salts, dried over anhydrous magnesium sulfate, and then concentrated to yield 3.59 g (84%) of **10**. The analytical sample was obtained by chromatography on a silica gel column using EtOH–methylene chloride (1:19) as eluent followed by recrystallization from a 3:1 mixture of methanol–benzene: mp 243–245 °C dec; M^+ = 306.1842 (calc 306.1831); ^1H NMR (pyridine-d_5) δ 2.12 (s, 2 H), 2.45 (br, 4 H), 2.64 (br, 4 H), 3.65 (m, 4 H, 4 OCH), 3.94 (m, 4 H, 4 OCH), 5.75 (dd, 4 H, J = 6.8, 4.9 Hz), 6.30 (dd, J = 9.0, 6.9 Hz, 4 OH, D_2O exch); ^{13}C NMR (pyridine-d_5) δ 38.50 (d), 43.04 (d), 46.49 (d), 61.67 (t), 131.5 (d).

(1α,2β,3α,6α,7β,8α)-4,5,9,10-Tetramethylenetetracyclo[6.2.2.2^{3,6}.0^{2,7}]tetradeca-11,13-diene (1). To a stirred, ice-cold solution of 0.80 g (2.61 mmol) of tetrol **10** in dry pyridine (15 mL) was added 3.98 g (15.6 mmol) of *p*-toluenesulfonyl chloride under a nitrogen atmosphere. The reaction mixture was allowed to stir at 0 °C for 6 h and then poured into cold 10% aqueous hydrochloric acid (60 mL). The aqueous solution was extracted with ether (3 × 100 mL). The combined etheral extracts were washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. Filtration and rotatory evaporation of the filtrate gave 1.87 g (78%) of the tetratosylate **11**. This material was used in the next step without further purification.

A solution of 1.87 g (2.03 mmol) of the prepared 11 in dry dimethyl sulfoxide (10 mL) was treated with 2.32 g (20.7 mmol) of potassium *tert*-butoxide. After the dark solution was stirred for 8 h at 50 °C, the reaction mixture was cooled to room temperature and water (40 mL) was added dropwise. The mixture was extracted with hexane (5 × 20 mL). The organic extract was dried over anhydrous magnesium sulfate and then evaporated in vacuo. The residue was chromatographed over silica gel using hexane as eluent to afford 0.26 g (43% from **10**) of 1 as colorless prisms (ether): mp 211–213 °C dec; M^+ = 234.1400 (calc 234.1409); IR (KBr) 3059, 3042, 2928, 2880, 1618, 902, 768, 692 cm^{-1}; UV (cyclohexane) λ_{max} = 243 nm (log ϵ = 4.41), 212 nm (shoulder, log ϵ = 4.08); ^1H NMR ($CDCl_3$) δ 2.33 (s, 2 H), 3.18 (dd, 4 H, J = 4.5, 3.3 Hz), 4.78 (s, 4 H), 5.12 (s, 4 H), 5.84 (dd, 4 H, J = 4.6, 3.2 Hz); ^{13}C NMR ($CDCl_3$) δ 42.57 (d), 47.22 (d), 102.4 (t), 130.6 (d), 147.4 (s). Anal. Calcd for $C_{18}H_{18}$: C, 92.26; H, 7.74. Found: C, 92.06; H, 7.79.

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Dichloromethane as Reactant in Synthesis: An Expedient Transformation of Prolinamide to a Novel Pyrrolo[1,2-*c*]imidazolone

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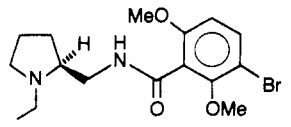
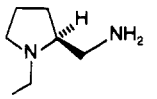
In the course of our work to achieve an efficient production method for the neuroleptic drug remoxipride (**1**),[2,3] we have been developing a new synthetic route for (*S*)-2-(aminomethyl)-1-ethylpyrrolidine (**2**), a crucial building block for **1** and for other pharmacologically interesting compounds.[4] Our favored synthesis[5] of **2** starts from



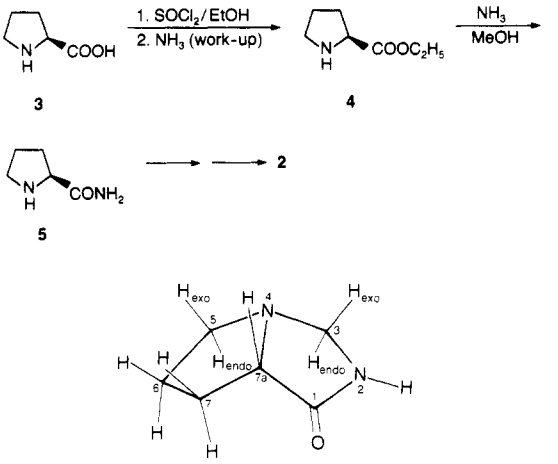
1



2

(*S*)-proline (**3**)[6] and proceeds in a virtually stereoconservative[7] fashion according to Scheme I. On certain occasions, especially when running large-scale experiments (e.g. in the pilot plant), we noted the formation of 3–4% (GC) of an impurity in the transformation of ester **4** to amide **5**. We now present the structure elucidation of the by-product as **6** and a mechanistic proposal for its formation.

Scheme I



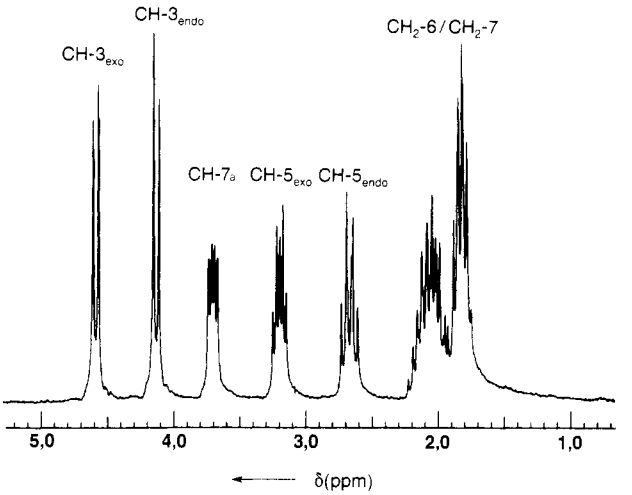


Figure 1. Right-hand part of ^1H NMR spectrum (200 MHz, $CDCl_3$) of **6**, with the indicated assignment of the signals.

Results and Discussion

To determine the source of the unknown impurity, we carefully reexamined the first two steps of the synthesis indicated in Scheme I. Thus, (*S*)-proline ethyl ester (**4**) is synthesized by following a standard procedure[8] from (*S*)-proline via the acid chloride. The subsequent amination is conducted under rather forced conditions using a large excess of NH_3 (10–15 equiv) in methanol at 40 °C (3 atm), which transforms the major part of **4** to its methyl ester[9] prior to being converted to amide **5**.

Comparison of our laboratory experience from these steps with the observed actual large-scale performance indicated that residual amounts of the dichloromethane used for extraction purposes during workup in the esterification step could be responsible for the impurity formation. Supporting evidence for this assumption was obtained when it was found that ordinary aminations of

(1) Present address: Astra Pain Control AB, Research & Development, Preclinical Research, S-151 85 Södertälje.

(2) Under clinical development by Astra Research Centre AB, S-151 85 Södertälje, Sweden. Remoxipride is the active principle in pharmaceutical preparations named Roxiam.

(3) See, e.g.: (a) Florvall, L.; Ögren, S.-O. *J. Med. Chem.* **1982**, *25*, 1280–86. (b) McCreadie, R. G.; Todd, N.; Livingstone, M.; Ecclestone, D.; Watt, J. A. G.; Tait, D.; Crocket, G.; Mitchell, M. G.; Huitfeldt, B. *Acta Psychiatr. Scand.* **1988**, *78*, 49–56.

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(5) (a) Federsel, H.-J.; Högberg, T.; Rämsby, S.; Ström, P. Swedish Patent Application 8 602 339-7, 1986. (b) Högberg, T.; Rämsby, S.; Ström, P. *Acta Chem. Scand.* **1989**, *43*, 660–64.

(6) Natural enantiomer (i.e. L configuration).

(7) Starting with (*S*)-proline of commercial quality (>99% ee; GC after N-derivatization with (*R*)-α-(methoxyphenyl)acetyl chloride followed by transformation of the carboxylic group to the methyl ester using diazomethane), **2** is obtained with an optical purity of ca. 95% ee (GC after NH_2 derivatization with the previously mentioned acid chloride).

(8) Deimer, K.-H. In *Methoden der organischen Chemie* (*Houben-Weyl*) 4th ed.; Georg Thieme Verlag: Stuttgart, 1974; Vol XV/1, p 315 ff.

(9) A kinetic study on the amination of (*S*)-*N*-ethylproline ethyl ester has been reported: Högberg, T.; Ström, P.; Ebner, M.; Rämsby, S. *J. Org. Chem.* **1987**, *52*, 2033–36.

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