Conversion of L-Pyroglutamic Acid to 4-Alkyl-Substituted L-Prolines. The Synthesis of *trans*-4-Cyclohexyl-L-proline

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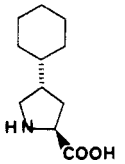
(*S*)-5-(Hydroxymethyl)-2-pyrrolidinone (**3**), prepared from L-pyroglutamic acid, was condensed with benzaldehyde to obtain the *O,N*-acetal **4** in excellent yield. Alkylation of **4** with 3-bromocyclohexene followed by reduction gave *trans*-4-cyclohexyl-L-prolinol (**7**) in good chemical yield with excellent stereoselectivity. Sequential N-protection, oxidation of the alcohol to the acid, and N-deprotection furnished *trans*-4-cyclohexyl-L-proline (**1**) in excellent yield and quality. Compound **1** serves as an intermediate for the preparation of ACE inhibitors including Fosenopril.

During a search for methods to prepare 4-alkyl-substituted L-prolines to support our ongoing ACE program[1], we reported a procedure[2] involving the interaction of lithium dialkylcuprates with 4-(tosyloxy)-L-prolines. Herein we describe a conceptually different approach (illustrated in Scheme I) to the preparation of *trans*-4-cyclohexyl-L-proline (**1**), an intermediate in the synthesis of Fosenopril.



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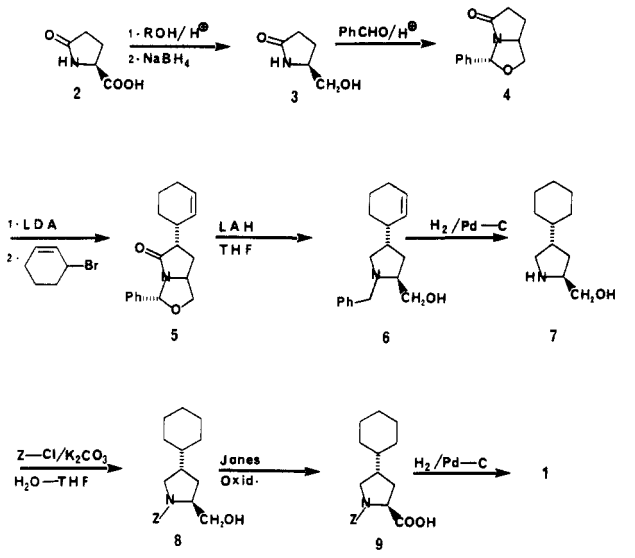
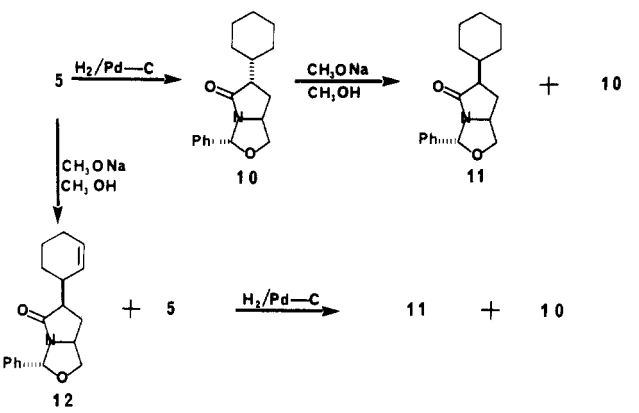
Scheme I depicts the sequence we developed for the synthesis of **1**. 5-(Hydroxymethyl)-2-pyrrolidinone (**3**), prepared from L-pyroglutamic acid by using the literature procedures,[3] served as the starting material. The strategy adopted for the synthesis of **1** features the protection of both active hydrogen atoms of **3** with a single protecting group that also serves to influence the stereochemistry of introduction of the 4-substituent. Intermediate **4** appeared to be ideal for this purpose. In compound **4**, the primary alcohol serves as a latent carboxylic acid. This approach was specifically chosen to avoid potential problems with maintaining Cl at the carboxylic acid oxidation state, e.g., selective enolate anion formation, complications involved with an enolate anion in the presence of an unprotected carbonyl group, and selective removal of the lactam carbonyl oxygen in the presence of the carboxylic acid.

Reaction of **3** with benzaldehyde in the presence of acid catalyst and with azeotropic removal of water produced the bicyclic *O,N*-acetal **4** as a single diastereomer[4] in 86% distilled yield. We have not proven the stereochemistry of the newly created asymmetric center in **4**; it is a single compound by spectroscopic methods, and we assume it has the stereochemistry as shown, on the basis of the literature precedent.[5] Reaction of the lithium enolate of **4**, prepared

Scheme I



Scheme II



by the action of LDA[6] on **4** in THF at −78 °C, with 3-bromocyclohexene (bromo- or iodocyclohexane did not give any desired reaction with the lithium enolate of **4**) produced **5** as a mixture of diastereomers. In order to examine the stereoselectivity of this alkylation, the double bond of **5** (which leads to an "extra" set of diastereomers) was removed by partial hydrogenation to give **10**. Spectroscopic analysis of **10** revealed that it is >95% a single isomer. Intentional isomerization of **10** using sodium

(1) (a) Petrillo, E. W., Jr.; Ondetti, M. A. *Med. Res. Rev.* **1982**, *2*, 1–41. (b) Petrillo, E. W., Jr. Eur. Pat. EP 063896, 1982. (c) Petrillo, E. W., Jr. Eur. Pat. EP 053902, 1982.

(2) Thottathil, J. K.; Moniot, J. L. *Tetrahedron Lett.* **1986**, *27*, 151.

(3) (a) Saigo, S.; Wada, M.; Himizu, J.; Ishida, A. *Chem. Pharm. Bull.* **1980**, *25*, 1449. (b) Silverman, R. B.; Levy, M. A. *J. Org. Chem.* **1980**, *45*, 815. (c) Schmidt, U.; Scholm, R. *Synthesis* **1978**, 753. (d) Faber, L.; Wiegrebe, W. *Helv. Chim. Acta* **1976**, *59*, 2201. (e) Bruim, J. W.; de-Koning, H.; Huisman, H. O. *Tetrahedron Lett.* **1975**, *15*, 4599.

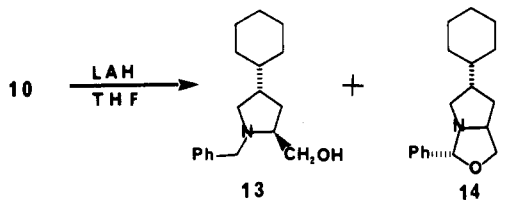
(4) Thottathil, J. K.; Przybyla, C.; Malley, M.; Gougoutas, J. Z. *Tetrahedron Lett.* **1986**, *27*, 1533.

(5) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390–5398.

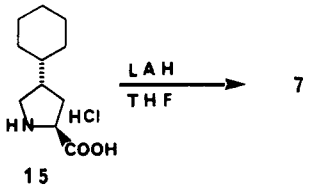
(6) Dr. F. Dursch and Dr. F. Okuniewicz of Squibb Chemical Process Technology have shown that $LiNH_2$ can be used successfully in place of LDA. We thank them for sharing this information.

0022-3263/86/1951-3140$01.50/0

Scheme III



Scheme IV



methoxide in methanol produced an almost 1:1 mixture of **11** and **10** by ^{13}C NMR analysis. Similarly, intentional isomerization of the diastereomers **5** using sodium methoxide in methanol produced a mixture of **12** and **5** which were clearly distinguishable by ^{13}C NMR analysis. Saturation of the double bonds of the mixture **12** and **5** gave the same mixture of **10** and **11** (Scheme II) as obtained from isomerization of **10**. This alkylation result is remarkable, both for the high stereoselectivity and the high chemical yield (cyclohexenyl bromide commonly gives cyclohexadiene during attempted displacement).

Proceeding with the synthesis of **1**, compound **5** was subjected to LAH reduction in THF to produce **6** as a mixture of diasteriomers. An identical reduction was carried out on pure **10** using excess LAH in refluxing THF to produce **13** as a single diasteriomer (Scheme III). Premature quenching of this reaction produced trace amounts of **14**, in addition to **13**, as indicated both by TLC monitoring and mass spectral analysis, and thus we assume that **14** is an intermediate in the formation of **13**. Compound **6** on hydrogenation/hydrogenolysis produced the amino alcohol **7** in 65% yield (from **4**) after crystallization. This material was analytically pure and devoid of any isomeric impurities. At this point the stereochemistry of the alkylation of **4** was confirmed by comparison of **7** with an authentic sample. LAH reduction of *trans*-4-cyclohexyl-L-proline hydrochloride (**15**) (Scheme IV), prepared by an independent method,[7] gave a sample of **7** identical in all respects with material prepared via the alkylation sequence described above.

Oxidation of the hydroxymethyl group of **7** to a carboxylic acid group completed the synthesis of **1**. This was best accomplished by use of an N-protection–oxidation–N-deprotection protocol, because of the difficulties in the isolation of **1** from the reaction mixture after the direct oxidation of **7** to **1**. Thus, reaction of **7** with benzyloxycarbonyl chloride in the presence of K_2CO_3 produced **8** in essentially quantitative yield. Jones oxidation of **8** produced **9**, which on catalytic hydrogenolysis followed by crystallization produced **1** in 70–80% overall yield from **7** identical in every respect with an authentic sample.[7]

In conclusion, we have described a new stereocontrolled route to the synthesis of *trans*-4-cyclohexyl-L-proline from inexpensive and readily available L-pyroglutamic acid. This method should also be applicable to other 4-alkyl-substituted prolines.[8] Our synthesis features the use of an oxazolidine ring as a bidentate protecting group and as a control element in the introduction of further stereochemical detail. Synthon **4** should find widespread applications for the synthesis of a wide variety of pyrrolidine derivatives.

Experimental Section

All reagents and solvents were used directly as purchased except THF, which was distilled from sodium benzophenone ketyl. With the exception of aqueous reactions, all reactions were conducted under N_2 or argon. Melting points were obtained on a Thomas-Hoover capillary apparatus and are uncorrected. Optical rotations were determined with a Perkin-Elmer 141 polarimeter. ^1H NMR spectra were recorded on either Jeol FX-270 or Jeol GX-400 instruments. Values are reported in δ units relative to Me_4Si. ^{13}C NMR spectra were recorded on a Jeol FX60-Q or Jeol FX-270 instrument and are reported in parts per million relative to the solvent except where noted. IR spectra were obtained on a Perkin-Elmer 257 spectrometer except for samples run in KBr, where a Perkin-Elmer 621 spectrometer was used. Analytical data were obtained by the Squibb Analytical Department.

(*S*)-5-(Hydroxymethyl)-2-pyrrolidinone (3) was prepared according to the literature[3] procedure: mp 84–86 °C; $[\alpha]_D$ +31.7° (*c* 5, EtOH).

***O,N*-Acetal 4.** A mixture of 85.0 g (0.70 mol) of alcohol **3**, 98.0 g (0.92 mol) of benzaldehyde, and 1.6 g (0.008 mol) of *p*-toluenesulfonic acid in toluene (500 mL) was refluxed under a Dean–Stark water separator with vigorous stirring in an oil bath. After 9 h the collection of water stopped. The cooled reaction mixture was washed with 5% sodium bicarbonate solution (2 × 50 mL), saturated sodium bisulfite solution (4 × 50 mL), water (2 × 50 mL), and brine (1 × 50 mL). The organic layer was dried over $MgSO_4$ and concentrated to afford an oil, which on distillation afforded 129 g (86%) of **4** as a colorless liquid: bp 145–150 °C (0.1 mm); $[\alpha]_D$ +269.6° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) 7.5–7.42 (2 H, m), 7.4–7.25 (3 H, m), 6.34 (1 H, S), 4.22 (1 H, dd, J = 8.0 and 6.4 Hz), 4.2–4.12 (1 H, m), 3.48 (1 H, t, J = 8.0 Hz), 2.85–2.76 (1 H, m), 2.58–2.50 (1 H, m), 2.41–2.32 (1 H, m) and 1.98–1.88 (1 H, m); ^{13}C NMR ($CDCl_3$) 177.80, 138.69, 128.20, 128.10, 125.66, 86.82, 71.34, 58.50, 33.09, 22.73; IR (neat) 1705 cm^{-1}. Anal. Calcd for $C_{12}H_{13}O_2N$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.97; H, 6.64; N, 6.72.

***trans*-4-Cyclohexyl-L-prolinol (7).** A solution of 12.9 mL (0.092 mol) of diisopropylamine in tetrahydrofuran (250 mL) was cooled to −10 °C, and 37.2 mL (0.092 mol) of *n*-butyllithium was added with vigorous stirring. The solution was then stirred for 15 min at −10 °C and cooled to −78 °C, and 18.7 g (0.092 mol) of acetal **4** in tetrahydrofuran (50 mL) was added with vigorous stirring. The mixture was stirred for another 30 min at −78 °C, and 16.5 mL (0.099 mol) of 3-bromocyclohexene[9] was added to the reaction mixture at −78 °C. The reaction temperature was raised to −20 °C; after 20 min TLC (silica gel, 4:1 EtOAc–hexane) indicated the absence of starting material. The reaction mixture was poured into crushed ice and water (400 mL), and sodium chloride was added to saturate the aqueous phase. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2 × 100 mL). The combined organic phase was washed with water (1 × 200 mL) and brine (1 × 200 mL), dried over $MgSO_4$, and concentrated to afford 26.0 g (100%) of semisolid **5**, as a mixture of diastereomers: ^{13}C NMR ($CDCl_3$) 179.87, 178.97, 138.83, 138.74, 130.09, 129.06, 128.42, 127.86, 126.63, 125.41, 87.71, 71.31, 70.69, 57.19, 56.94, 48.96, 48.40, 36.91, 36.63, 27.51, 24.55, 24.35, 23.43, 21.45, and 21.20. Compound **5** obtained above was used for the next step without further purification. A solution of 24.0 g (0.085 mol) of **5** in tetrahydrofuran (100 mL) was added dropwise to a gently refluxing suspension of 4.8 g (0.126 mol) of LAH in tetrahydrofuran (50 mL). After the addition was complete, the reaction mixture was refluxed for 1 h, cooled in an ice

(7) *trans*-4-Cyclohexyl-L-proline hydrochloride (**15**) was prepared by the hydrogenation of *trans*-4-phenyl-L-proline[2] in ethanolic HCl by using PtO_2 catalyst.

(8) For recent references to 4-alkyl-substituted prolines, see: (a) Nakajima, M.; Torikata, A.; Tamaoki, H.; Haneishi, T.; Arai, M.; Kinoshita, T.; Kuwano, H. *J. Antibiot.* **1983**, *36*, 967. (b) Fukushima, K.; Arai, T.; Mori, Y.; Tsuboi, M.; Suzuki, M. *Ibid.* **1983**, *36*, 1612. (c) Birkenmeyer, R. D. Kagan, F. *J. Med. Chem.* **1970**, *13*, 616.

(9) Purchased from Alfa Products of Morton Thiokol Inc.

bath, and saturated sodium sulfate solution was added dropwise slowly and carefully until a white granular precipitate was formed. The mixture was diluted with ethyl acetate (200 mL) and filtered through a Celite pad, and the residue was washed thoroughly with ethyl acetate. The combined filtrate was dried over $MgSO_4$ and concentrated to obtain 22.9 g (100%) of **6**, a thick oil, as a mixture of diastereomers: ^{13}C NMR ($CDCl_3$) 139.02, 129.65, 129.56, 128.58, 128.08, 127.55, 127.50, 126.77, 64.19, 64.08, 62.30, 59.03, 58.73, 58.59, 42.38, 39.61, 39.45, 32.98, 32.56, 28.04, 27.70, 25.08, 21.28, and 21.09.

The 22.9 g of **6** obtained above was dissolved in 90 mL of ethyl acetate–glacial acetic acid (1:2), 2.5 g of 10% Pd–C was added, and the mixture was shaken under hydrogen at 45 psig. After 2 h the catalyst was removed by filtration, and the filtrate was concentrated. The residue was dissolved in water (100 mL) and the solution basified by the addition of 30% aqueous NaOH solution with vigorous mechanical stirring. The precipitated cottony material was filtered, washed with water (100 mL), and air-dried to give 15.0 g of crude **7**. Crystallization from toluene–hexane yielded 10.0 g (65% from **4**) of analytically pure **7**: mp 98–100 °C; $[\alpha]_D$ +12.9° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) 3.58–3.45 (1 H, m), 3.38–3.26 (2 H, m) 3.15–3.07 (1 H, dd, J = 10.2 and 7.2 Hz), 2.59 (1 H, t, J = 9.8 Hz), 2.5–2.4 (2 H, br, exchanges with D_2O), 1.88–1.58 (7 H, m), 1.55–1.43 (1 H, m) 1.28–1.03 (4 H, m), and 1.02–0.86 (2 H, m); ^{13}C NMR ($CDCl_3$) 65.11, 59.28, 51.16, 45.14, 42.18, 32.08, 31.97, 31.86, 26.39, and 26.14; IR (KBr) 3484, 2985, 2925, 2854, 2794, 2750, 2719, 1518, and 1428 cm^{-1}. Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 71.88; H, 11.26; N, 7.32.

***trans*-4-Cyclohexyl-L-proline (1).** A solution of 45.0 g (0.246 mol) of the amino alcohol **7** in THF (400 mL) was added to a solution of 18.7 g (0.135 mol) of K_2CO_3 in water (120 mL), and the solution was cooled to −2 °C in an ice–salt bath. Benzyloxycarbonyl chloride (36.0 mL, 0.252 mol) was added dropwise to the well-stirred reaction mixture, with the internal temperature kept between −2 and 0 °C. After the addition was complete (20 min), the reaction mixture was stirred for 15 min at 0 °C and then poured into crushed ice and water (500 mL). Sodium chloride was added to saturate the aqueous phase. The organic phase was separated and the aqueous phase extracted with ethyl acetate (3 × 100 mL). The combined organic phase was washed with 5% aqueous HCl (2 × 100 mL), water (1 × 100 mL), and brine (1 × 100 mL). The organic layer was dried over $MgSO_4$ and concentrated to obtain **8** (77.9 g) as a colorless thick oil: $[\alpha]_D$ −21.0° (*c* 1, $CHCl_3$); ^{13}C NMR ($CDCl_3$) 156.88, 136.56, 128.42, 127.95, 127.86, 67.10, 66.87, 60.26, 51.25, 43.19, 41.76, 32.47, 31.83, 31.36, 26.27, and 26.03. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.88; H, 8.58; N, 4.37.

The 77.9 g of **8** obtained above was dissolved in acetone (400 mL) and added dropwise to a stirred solution of Jones reagent[10] (190 mL) in acetone (500 mL) at −5 °C. After the addition was complete (3 h), the reaction mixture was stirred for 3 more h at −5 °C. Isopropyl alcohol (30 mL) was added to the mixture, and it was stirred for 30 min. The acetone layer was decanted, concentrated to a thick oil, and recombined with the residue in the flask. After dilution with water to a volume of 1500 mL, the mixture was extracted with ethyl acetate (4 × 200 mL). The combined organic phase was washed with water (1 × 100 mL) and brine (1 × 100 mL), dried over $MgSO_4$, and concentrated to give **9** as a glassy solid (78.4 g). An analytical sample was prepared by dissolving **9** in toluene and washing with 5% KOH solution. Acidification of the water layer, reextraction, and solvent evaporation gave pure **9**: $[\alpha]_D$ −49.1° (*c* 1, $CHCl_3$); ^{13}C NMR ($CDCl_3$) 177.75, 176.60, 155.50, 154.34, 136.29, 128.36, 128.25, 127.95, 127.83, 127.72, 127.47, 67.35, 67.01, 59.48, 58.98, 50.94, 50.,63, 43.24, 42.21, 41.51, 34.76, 33.51, 31.69, 31.25, 26.17, and 25.92. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.6; N, 4.22. Found: C, 68.97; H, 7.55; N, 4.23.

The 78.4 g of the crude acid **9** was dissolved in methanol (600 mL), and 10.0 g of Pd–C (10%) was added. The mixture was stirred under 1 atm of hydrogen at ambient temperature. After 2 h the catalyst was filtered, and the solvent was removed to obtain a white solid, which was powdered and suspended in ethyl acetate (200 mL). The mixture was heated to 60 °C for 10 min and then filtered. The resulting solid was washed with ethyl acetate (200 mL) to give 41.8 g (86.3%) of **1** as a white solid: mp 250–253 °C; $[\alpha]_D$ −30.3° (*c* 1, acetic acid). Recrystallization of the above material from water–methanol gave 37.6 g (77.7% from **7**) of white shiny plates of **1**: mp 265–267 °C; $[\alpha]_D$ −32.0° (*c* 1, acetic acid); ^1H NMR (CD_3OD) 4.06–4.03 (1 H, m), 3.58–3.53 (1 H, m), 2.86 (1 H, t, J = 10 Hz), 2.36–2.32 (1 H, m), 1.99–1.85 (3 H, m), 1.79–1.66 (4 H, m), 1.33–1.13 (4 H, m), and 1.07–0.95 (2 H, m); ^{13}C NMR (CD_3CO_2D) 174.82, 61.82, 50.72, 43.97, 41.43, 33.98, 32.47, 32.11, 26.86, and 26.67; IR (KBr) 3379, 3294, 3063, 2933, 2850, 2789–2358, 1620, 1447, 1366, and 1288 cm^{-1}. Anal. Calcd for $C_{11}H_{19}NO_2 \cdot 0.18H_2O$: C, 65.87; H, 9.76; N, 6.98. Found: C, 65.87; H, 9.76; N, 6.71.

LAH Reduction of *trans*-4-Cyclohexyl-L-proline Hydrochloride (15) to 7. To a suspension of 0.25 g (0.006 mol) of LAH in THF (20 mL) was added 0.5 g (0.002 mol) of solid *trans*-4-cyclohexyl-L-proline hydrochloride (**15**) in portions with vigorous stirring and ice cooling. After the addition the reaction mixture was refluxed for 4 h and then cooled in an ice bath. Ethyl acetate was added dropwise slowly and carefully until the vigor of the reaction subsided. Further addition of saturated sodium sulfate solution gave a white granular precipitate. The mixture was diluted with ethyl acetate (20 mL) and filtered through a Celite pad. The residue was washed thoroughly with ethyl acetate. The combined filtrate was dried over $MgSO_4$ and concentrated to obtain 0.38 g of crude **7**. Crystallization from ether–hexane yielded 0.2 g (51%) of **7**, which was identical in every respect with the sample prepared from **5**.

Reduction of 5 to 10. To a solution of 1.0 g (0.0035 mol) of crude **5** in ethyl acetate (25 mL) was added 0.1 g of 10% Pd–C, and the mixture was stirred under hydrogen at ambient temperature and atmospheric pressure. After 1 h the catalyst was removed by filtration. The filtrate was concentrated to give a white solid, which was purified by passage through a silica gel column to obtain 0.8 g of **10** as a white solid (80% from **4**): mp 69–71 °C; $[\alpha]_D$ +166.2° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) 7.44–7.42 (2 H, m), 7.37–7.25 (3 H, m), 6.32 (1 H, S), 4.22–4.19 (1 H, dd, J = 6.2 and 7.2 Hz), 4.04–3.97 (1 H, m), 3.39 (1 H, t, J = 8.5 Hz), 2.64–2.59 (1 H, m), 2.19–2.12 (1 H, m), 2.03–1.94 (1 H, m), 1.82–1.65 (6 H, m), and 1.2–1.1 (5 H, m); ^{13}C NMR ($CDCl_3$) 179.98, 139.05, 128.28, 125.82, 87.24, 71.62, 57.64, 50.63, 39.64, 30.60, 28.93, 26.25, 26.11, and 25.33; IR (KBr) 1712 cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.9. Found: C, 76.00; H, 7.99; N, 5.08.

Epimerization of 10 to a Mixture of 11 and 10. To a solution of 0.3 g (0.001 mol) of **10** in THF (5 mL) was added a solution of 0.06 g (0.001 mol) of sodium methoxide in methanol (0.25 mL). The mixture was stirred at ambient temperature for 18 h, diluted with water (50 mL), and extracted with ethyl acetate (3 × 25 mL). The combined organic phase was washed with water (1 × 25 mL) and brine (1 × 25 mL), dried over $MgSO_4$, and concentrated to obtain 0.3 g of a thick oil (an almost 1:1 mixture of **11** and **10**): ^{13}C NMR ($CDCl_3$) 179.87, 177.69, 138.74, 128.14, 125.80, 125.69, 87.10, 86.46, 72.01, 71.45, 57.47, 56.16, 50.48, 50.10, 39.50, 37.35, 31.13, 30.46, 28.82, 28.40, 27.51, 26.17, 25.97, and 25.16.

Epimerization of 5 to a Mixture of 12 and 5. To a solution of 3.0 g (0.011 mol) of **5** in THF (25 mL) was added a solution of 0.6 g (0.011 mol) of sodium methoxide in methanol (2.5 mL). The reaction mixture was stirred at ambient temperature for 12 h. The reaction mixture was diluted with water (200 mL) and extracted with ethyl acetate (3 × 75 mL). The combined organic phase was washed with water (1 × 50 mL) and brine (1 × 50 mL), dried over $MgSO_4$, and concentrated to obtain 3.0 g of a thick oil (an almost 1:1 mixture of **12** and **5**): ^{13}C NMR ($CDCl_3$) 180.15, 179.25, 177.41, 177.22, 139.05, 138.71, 130.37, 130.20, 129.42, 128.67, 128.36, 128.14, 127.47, 126.86, 125.80, 125.66, 87.32, 87.02, 86.49, 72.15, 71.98, 71.62, 71.03, 57.50, 57.25, 56.27, 56.13, 49.30, 49.18, 48.77, 37.19, 36.94, 35.43, 35.04, 27.81, 26.86, 24.88, 24.69, 23.80, 21.70, and 21.51.

Reduction of the Diastereomeric Mixtures of 12 and 5 to a Mixture of 11 and 10. To a solution of 1.0 g (0.0085 mol) of the crude mixture of **12** and **5** in ethyl acetate (25 mL) was added 0.1 g of 10% Pd–C, and the mixture was stirred under 1 atm of hydrogen at ambient temperature. After 1 h the catalyst was removed by filtration. The filtrate was concentrated to give 1.0 g of a thick oil (an almost 1:1 mixture of **11** and **10**) indistinguishable from the mixture obtained by the epimerization of **10**.

(10) Prepared by dissolving 26.7 g of CrO_3 in 23 mL of concentrated H_2SO_4 and diluting to 100 mL with water.

LAH Reduction of 10 to 13. A solution of 0.5 g (0.0017 mol) of **10** in THF (10 mL) was added to a gently refluxing suspension of 0.1 g (0.0026 mol) of LAH in THF (10 mL). After the addition the reaction mixture was refluxed for 1 h and then cooled in an ice bath. Saturated sodium sulfate solution was added dropwise slowly and carefully until a white granular precipitate was formed. The mixture was diluted with ethyl acetate (25 mL) and filtered through a Celite pad. The residue was washed thoroughly with ethyl acetate. The combined filtrate was dried over $MgSO_4$ and concentrated to obtain 0.46 g (96%) of **13** as a thick oil: ^{13}C NMR ($CDCl_3$) 138.08, 128.50, 128.06, 126.77, 64.11, 62.46, 59.17, 58.73, 43.34, 42.49, 33.14, 31.72, 31.61, 26.31, and 25.99.

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Electrogenerated Base (EG Base) Induced Hydroxymethylation of the Side Chain of Nitroalkylbenzenes with Paraformaldehyde

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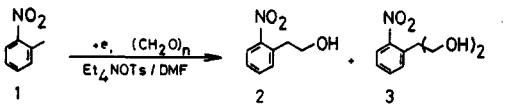
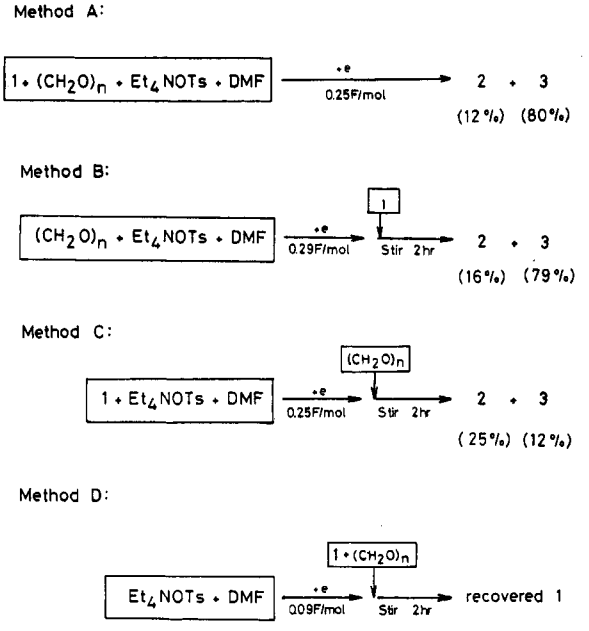
Hydroxymethylation of nitroalkylbenzenes with paraformaldehyde was accomplished by electrolysis in a $(CH_2O)_n$–DMF–Et_4NOTs–(Pt electrode) system. The reaction was found to be catalytic (0.25 faraday/mol) and dependent on the electroreduction of formaldehyde and/or nitroalkylbenzene. A variety of nitroalkylbenzenes were transformed to their corresponding mono- and/or bishydroxymethylated derivatives in good yield. The product yield and selectivity were shown to depend on the order of reagent addition, solvent, supporting electrolyte, and structure of the starting nitroalkylbenzenes. A plausible mechanism of the generation of base catalysts (EG base) in electroreductive media is discussed.

Homologation of the alkyl chain of nitroalkylbenzenes is an essential procedure for derivatization of readily accessible nitroalkylbenzenes into useful intermediates.[1] Among various kinds of approaches, hydroxymethylation of nitroalkylbenzenes with paraformaldehyde is a powerful procedure for this purpose and has been extensively investigated by use of a variety of bases, such as KO-*t*-Bu,[2] NaOMe,[3] KOH,[4] NaOH,[4] KOH- or NaOH-crown ether,[5] alkali phenolate,[6] tetraalkylammonium hydroxide,[7] DBU,[7] and NaCN.[8] However, due to the low conversion of the starting materials and/or the lack of the product selectivity, there still remain difficulties in obtaining mono- or bishydroxymethylation products from the nitroalkylbenzenes in satisfactory yields.

Scheme I



Scheme II



Incidentally, electrochemically generated bases (EG base) in the electroreductive media have received much attention from both the mechanistic and synthetic points

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(6) Morimoto, T.; Hashimoto, I.; Yamaoka, H. Japanese Patent 77 108 941, 1977; *Chem. Abstr.* **1978**, *88*, 104875.

(7) Morimoto, T.; Hashimoto, I.; Yamaoka, H. Japanese Patent 77 139 035, 1977; *Chem. Abstr.* **1978**, *88*, 104876.

(8) Tungler, A.; Bende, Z.; Petro, J.; Mathe, T. Hung, Pat. 30 628, 1984; *Chem. Abstr.* **1984**, *101*, 90566.

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