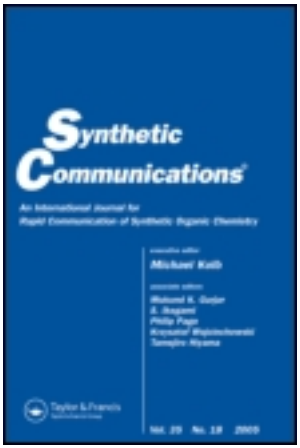

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Synthesis of a new, C 2 Symmetric α,α - Bis-(Carboxymethyl) Substituted Nitroxide

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SYNTHESIS OF A NEW, C_2 SYMMETRIC α,α' - BIS-(CARBOXYMETHYL) SUBSTITUTED NITROXIDE

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Abstract. The novel, diastereomeric *meso*- (*cis*) and (±)- (*trans*) nitroxides 2,5-dicarboxymethyl-2,5-dimethylpyrrolidine-1-oxyl have been synthesized *via* a dienolate based strategy. Both optically pure enantiomers of the C_2 symmetric *trans* diastereomer have been obtained *via* resolution of the corresponding amine with dibenzoyltartaric acid.

Introduction.

Recently, chiral nitroxides have aroused increasing interest, as new and promising applications have emerged in various fields of chemistry,[1] such as enantioselective oxidation catalysis,[2] the development of paramagnetic chiral liquid crystals,[3] or coupling reactions with prochiral radicals.[4] We have previously reported the synthesis of stable nitroxides of the piperidine series, bearing respectively an ester and a methyl substituent at the α and α' positions.[5] The key step of the synthesis involved dienolate species located α,α' to a Boc protected nitrogen atom. This strategy furnished a mixture of *meso* (*cis*) and (±) (*trans*) *N*-protected 2,5-

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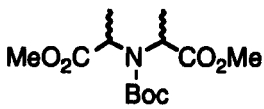
dicarboxymethyl-2,5-dimethylpiperidine in nearly equal amounts. After separation, *N*-deprotection and oxidation, the corresponding *meso* and (±) nitroxides have been obtained. We describe herein the extension of this strategy to the pyrrolidine series.

Synthesis of *meso* and (±) pyrrolydinyl nitroxides.

Early attempts involved reaction of 1,2-diiodo- or dibromoethane with the dienolate prepared from diester **1**.[5] Complex mixtures were obtained, from which none of the desired pyrrolidine was isolated, under any of the experimental conditions.



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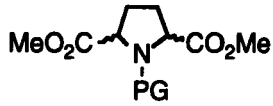
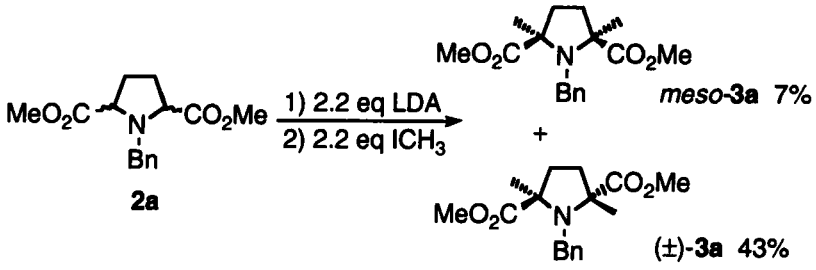


2a (PG = Bn)

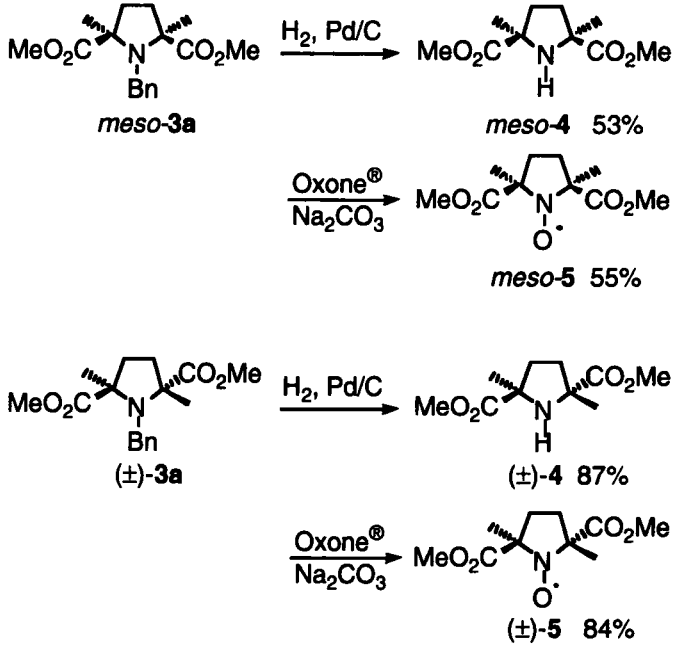
2b (PG = )

We turned next to a complementary approach, involving the dienolate of *N*-protected pyrrolidine diesters **2**. *N*-Benzyl-2,5-dicarboxymethyl pyrrolidine **2a** was readily obtained via Hoffmann reaction of dimethyl-2,5-dibromoadipate with benzylamine.[6] This method furnished pyrrolidine **2a** directly in a protected form (PG = Bn), as a 1:2 mixture of *meso*/(±) diastereomers, easily separable by column chromatography. When *meso*-**2a** was treated with LDA (2.2 eq), followed by iodomethane (2.2 eq), a 50% yield of dimethylated product **3a** was obtained, as a 1:6 mixture of *meso*/(±) diastereomers, which were easily separated by column chromatography.[7] Not surprisingly, **3a** was also obtained with the same yield and diastereomeric ratio starting from (±)-**2a**. Therefore, **2a** was more conveniently used directly as a mixture of diastereomers in the metallation step (Scheme 1).



Scheme 1

Deprotection of chromatographically separated *meso*- and (±)-**3a** (H_2, Pd/C) furnished pure diasteromeric amines **4** which after oxidation (Oxone®, Na_2CO_3) gave *meso*- and (±)-nitroxides **5** (Scheme 2).



Scheme 2

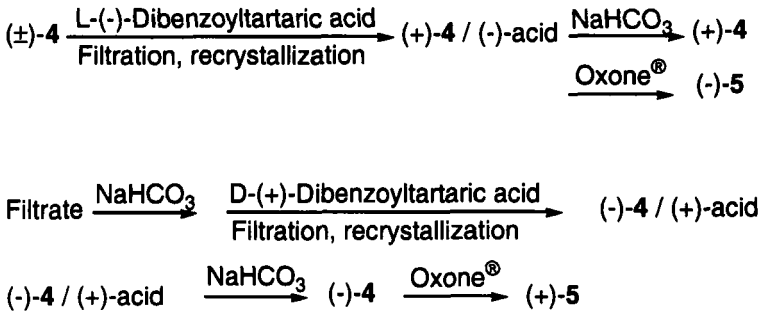
These novel nitroxides were obtained as orange oils which exhibited ESR spectra with triplet hyperfine structures (*meso*-**5** : g = 2.0072, a_N [G] = 13.1. (±)-**5** : g = 2.0066, a_N [G] = 12.9). Both were of lower stabilities than the corresponding piperidine analogues,[5] as they showed slow degradation when stored for several weeks at room temperature. They are best stored in the dark in the refrigerator.

Synthesis of enantiomerically pure (+)- and (-)-5.

We were next interested in obtaining C_2 symmetric nitroxides **5** in their optically pure forms. In a first attempt the *N*-benzyl protecting group was replaced by an α-methyl benzyl group (**2b**). The presence of a new stereogenic centre of fixed absolute configuration could lead to asymmetric induction during dienolate alkylation. It could also provide an easy access to pure enantiomers of the (±) amine **4**, since their precusors would be diastereomers. Hoffmann reaction of dimethyl-2,5-dibromoadipate with (S)-(-)-α-methylbenzylamine furnished **2b** in 60% yield as a 2:1:1 mixture of diastereomers. Their separation being difficult, **2b** was used as a mixture in the next step: it was treated with 2.2 eq LDA for 5 h at 0°C,[8] followed by addition of iodomethane. The crude material obtained after workup contained five products, unseparable by standard column chromatography. GC-MS analysis revealed that the three main products were monomethylated and that dimethylated products were present in only minor amounts. A second LDA-iodomethane treatment of the crude mixture[5] led to extensive degration; several variations of the metallation step using other strong bases, solvents or temperature conditions did not give better results. Even if more powerful separation techniques (for example preparative HPLC) could possibly allow isolation of small amounts of the desired products, this method would be of little preparative value.

We have therefore undertaken resolution of the (±) amine **4** via fractional crystallization of the diastereomeric salts formed with optically active carboxylic

acids. The best results were obtained using dibenzoyltartaric acid, commercially available in either enantiomerically pure form. L-(-)-dibenzoyltartaric acid gave a crystalline salt with (±)-**4** in dichloromethane. After one recrystallization of this salt from acetone followed by alkaline treatment (saturated solution of $NaHCO_3$), optically pure (+)-**4** (ee > 98%)[9] was obtained showing a specific rotation of $[\alpha]_D^{21}$ = + 17.2 (c 1.2, EtOAc). The mother liquors furnished, after alkaline treatment, amine **4** enriched in the (-) enantiomer. This sample was treated with D-(+)-dibenzoyltartaric acid and processed as before, giving optically pure (-)-**4** (ee > 98%;[9] $[\alpha]_D^{21}$ = - 17.3 (c 1.6, EtOAc)). Both enantiomers of amine **4** were next oxidized to the corresponding optically pure nitroxides ((+)-**4** gave (-)-**5** with $[\alpha]_D^{21}$ = - 71.4 (c 0.97, EtOAc) and (-)-**4** gave (+)-**5**, ($[\alpha]_D^{21}$ = + 71.6 (c 1.1, EtOAc)),[10] isolated as orange oils (Scheme 3).



Scheme 3

The absolute configurations of these novel optically active amines and nitroxides remain unknown. Efforts to crystallize derivatives of optically pure amine **4** containing heavy atoms or additional asymmetric centers of known configuration suitable for X-ray analysis have failed.

Conclusion

In summary, we have extended our dienolate-based strategy to the pyrrolidine series, obtaining the (±) compounds with good diastereoselectivity. Both optically pure enantiomers of a novel, C_2 symmetric pyrrolidinyl nitroxide have been obtained *via* resolution of the corresponding amine. The approach used here should be easily scaled up and could make these new optically active nitroxides available in substantial amounts. Synthetic applications of these compounds and of analogues obtained by chemical transformations of the ester groups are under investigation.

Experimental

Organometallic reactions were performed under an oxygen free atmosphere of argon with exclusion of moisture from reagents and glassware. The solvents were dried using standard methods prior to use. Analytical thin layer chromatography (TLC) was performed using Merck 60F 254 plates. Visualization of the developed chromatogram was performed by UV absorbance or ethanolic phosphomolybdic acid. Column chromatography was performed using Merck Geduran Si 60 silica gel (0.040 - 0.063 mm) with the indicated solvent system. Optical rotations were measured on Perkin Elmer 214 or 341 polarimeters. GLC analyses were performed with a Perkin Elmer Autosystem apparatus with a flame ionization detector using a 0.2 mm x 30 m OV 17 capillary column. Infrared spectra were recorded on a Perkin Elmer IR 397 or a Nicolet Impact 400 spectrometer. ^{1}H NMR spectra were recorded on a Bruker AC200 or a Bruker WM250 spectrometer (200 and 250 MHz respectively). Chemical shifts are reported in ppm on the δ scale relative to tertramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were also recorded on a Bruker AC200 or a Bruker WM250 (50 and 62.5 MHz respectively) with complete proton decoupling. Chemical shifts are reported in ppm relative to

tetramethylsilane on the δ scale. Mass spectra were obtained on a Nermag mass spectrometer. EPR spectra were recorded at room temperature on a Bruker ESP 300E spectrometer. UV-vis spectra were recorded on a Kontron Instruments Uvikon 930 spectrometer. Melting points have been determined on a Büchi 530 apparatus and are uncorrected. Elemental analyses were performed at the Service Central d'Analyses of the C.N.R.S. in Vernaison.

1-Benzyl-2,5-dicarboxymethyl-2,5-dimethylpyrrolidine (3a)

A solution of 1-Benzyl-2,5-dicarboxymethylpyrrolidine[6] (3.48 g, 12.6 mmol, used as a 1:2 mixture of *meso*/(±) diastereomers) in 32 mL of anhydrous THF, was added dropwise to a solution of 25.2 mmol LDA in THF (49.5 mL of a 0.51 M solution),[11] at -78°C. The mixture was stirred at the same temperature for 1 h. Iodomethane (1,6 mL, 25.7 mmol) was then added dropwise. The initially dark red coloured solution turned yellow during addition. Temperature was raised slowly to room temperature and stirring was maintained overnight. THF was then removed at reduced pressure. Water (100 mL) was added to the residue. The aqueous phase was extracted twice with ether, the combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure, leaving a yellow oil (3.8 g). The crude products was purified by column chromatography on silica gel (hexanes/EtOAc, 98:2). The first eluted diastereomer was (±)-**3a** (1,63 g, 43%), obtained as a colorless oil; ^{1}H NMR (250 MHz) δ ($CDCl_3$) 1.45 (s, 6H), 1.89 - 2.19 (m, 4H), 3.50 (s, 6H), 3.88 (d, 1H J = 15.5 Hz), 4.04 (d, 1H, J = 15.5 Hz), 7.13 - 7.27 (m, 5H); ^{13}C NMR (62.5 MHz) δ ($CDCl_3$) 22.7, 37.2, 48.0, 51.4, 68.3, 125.5, 127.7, 128.3, 140.4, 176.8; IR (neat) cm^{-1} 3026, 2981, 2949, 1732, 1454, 1433, 1279, 1255, 1195, 1168, 1147, 1066; MS (DCI, NH_3 + isobutane) m/z 306 (100), 246 (24). *meso*-**3a** was eluted next (0.280 g, 7%), colorless oil; ^{1}H

NMR (250 MHz) δ ($CDCl_3$) 1.26 (s, 6H) 1.73 - 1.76 (m, 2H), 2.41 - 2.44 (m, 2H), 3.65 (s, 6H), 4.09 (s, 2H), 7.20 - 7.36 (m, 5H); ^{13}C NMR (62.5 MHz) δ ($CDCl_3$) 24.8, 35.7, 48.2, 51.3, 68.5, 126.3, 127.8, 128.5, 142.3, 175.7; IR (neat) cm^{-1} 3030, 2976, 2959, 1729, 1457, 1256, 1230, 1199, 1162, 1128; MS (DCI, NH_3 + isobutane) m/z 306 (100), 246 (31).

(±)-2,5-Dicarboxymethyl-2,5-dimethylpyrrolidine ((±)-4)

Palladium on charcoal (0.16 g, 10% Pd/C) was added to a solution of (±)-**3a** (1.0 g, 3.28 mmol) in 8 mL ethanol. The black suspension was vigorously stirred overnight under a hydrogen atmosphere (balloon). The suspension was filtered and the filtrate evaporated under reduced pressure. The crude product was purified by column chromatography over silica gel (hexanes/EtOAc, 80:20) giving pure (±)-**4** as a colorless liquid (0.61 g, 87%); bp (0.75 mm Hg) 70°C; ^1H NMR (250 MHz) δ ($CDCl_3$) 1.42 (s, 6H), 1.66 - 1.79 (m, 2H), 2.26 - 2.37 (m, 2H), 2.73 (bs, 1H), 3.73 (s, 6H); ^{13}H NMR (62.5 MHz) δ ($CDCl_3$) 25.9, 36.8, 52.2, 66.3, 177.4; IR (neat) cm^{-1} 3358, 2976, 2953, 2875, 1731, 1450, 1435, 1289, 1266, 1196, 1160; MS (DCI, NH_3 + isobutane) m/z 216 (100), 156 (29).

***meso*-2,5-Dicarboxymethyl-2,5-dimethylpyrrolidine (*meso*-4)**

The same procedure as above was applied to *meso*-**3a** (153 mg), 0.5 mmol) dissolved in 2 mL ethanol and using 20 mg of Pd/C. After column chromatography purification *meso*-**4** (57 mg, 53%) was isolated as a colorless liquid; ^1H NMR (200MHz) δ ($CDCl_3$) 1.39 (s, 6H), 1.71 - 1.87 (m, 2H), 2.17 - 2.32 (m, 2H), 3.28 (bs, 1H), 3.69 (s, 6H); ^{13}C NMR (62.5 MHz) δ ($CDCl_3$) 27.4, 35.4, 52.1, 65.8, 177.0; IR (neat) cm^{-1} 3362, 2976, 2953, 1732, 1454, 1286, 1248, 1198, 1113; MS (CDI, NH_3 + isobutane) m/z 216 (100), 156 (26).

(±)-2,5-Dicarboxymethyl-2,5-dimethylpyrrolidine-1-oxyl ((±)-5)

Oxone® (1.22 g, 2 mmol) was added in portions of ca 200 mg every 10 min, to a well stirred mixture of (±)-**4** (215 mg, 1 mmol) and Na_2CO_3 (1.06 g, 10 mmol) in 2 mL ethanol and 1 mL water. At the end of the addition, the mixture was stirred for another 5 h. The solid was then filtered off and washed with ethanol. The combined filtrate and washings were evaporated at reduced pressure, and the residue was chromatographed on silica gel (hexane/EtOAc, 90:10), affording (±)-**5** as an orange oil (193 mg, 84%); IR (neat) cm^{-1} 2995, 2956, 1749, 1733, 1457, 1373, 1286, 1203, 1178, 1080; MS (DCI, NH_3 + isobutane) m/z 232 (100), 172 (83); UV-vis (2.10^{-3} M in CH_2Cl_2) 240 nm (ε = 2640), 434 nm (ε = 3); ESR ($1.08.10^{-3}$ M in toluene) g = 2.0066, a_N = 12.9 G. Anal. Calcd. for $C_{10}H_{16}NO_5$: C, 52.19; H, 6.79; N, 6.00. Found = C, 52.17; H, 7.00; N, 6.08.

***meso*-2,5-Dicarboxymethyl-2,5-dimethylpyrrolidine-1-oxyl (*meso*-5)**

The same procedure as above was applied to *meso*-**4** (43 mg, 0.2 mmol), giving *meso*-**5** (25 mg, 55%) as a orange oil; IR (neat) cm^{-1} 2989, 2956, 1735, 1469, 1369, 1290, 1205, 1171, 1139; MS (DCI, NH_3 + isobutane) m/z 232 (31), 172 (100); UV-vis ($1.61.10^{-4}$ M in CH_2Cl_2) 247 nm (ε = 2088), 432 nm (ε = 3); ESR (0.87 10^{-3} M in toluene) g = 2.0072, a_N = 13.1 G. Anal. Calcd. for $C_{10}H_{16}NO_5$ = C, 52.19; H, 6.79; N, 6.00. Found = C, 52.02; H, 6.95; N, 6.11.

Resolution of (±)-4

A warm solution of L-(-)-dibenzoyltartaric acid (1.6 g, 4.46 mmol) in 15 mL of dichloromethane was added to a solution of (±)-**4** (1 g, 4.46 mmol) in 2 mL dichloromethane. The solution was left at -25°C overnight. The white crystals which have deposited were filtered and dried. They were redissolved in boiling

acetone. This solution was left at room temperature overnight, giving 264 mg of crystals. They were dissolved in 10 mL of a saturated solution of $NaHCO_3$. The aqueous solution was extracted with ether, the combined organics dried with Na_2SO_4 and evaporated at reduced pressure leaving (+)-**4** (101 mg, 20% of the theoretical yield); ee > 98%,[9] $[\alpha]_D^{21}$ = + 17.2 (c 1.2, EtOAc). The combined mother liquors were evaporated under reduced pressure. The solid was treated with 100 mL of saturated $NaHCO_3$. Etheral extraction and workup as above furnished amine **4** enriched in the (-) enantiomer (825 mg, 3.84 mmol). It was dissolved in 2 mL dichloromethane, and mixed with a warm solution of D-(+)-dibenzoyltartaric acid (1.38 mg, 3.84 mmol) in 16 mL of dichloromethane. After one night at +4 °C, 953 mg of crystals were obtained. They were dissolved in boiling acetone; this solution was left overnight at room temperature, leaving 624 mg of crystals, which after alkaline treatment (see above) furnished (-)-**4** (205 mg, 41% of the theoretical yield); ee > 98%;[9] $[\alpha]_D^{21}$ = - 17.3 (c 1.6, EtOAc).

Synthesis of (+)- and (-)-5

The same oxidation procedure was used as for the oxidation of (±)-**4** (see above). Starting from enantiomerically pure (+)-**4** (80 mg, 0.35 mmol), (-)-**5** was obtained (70 mg, 82%) $[\alpha]_D^{21}$ = - 71.4 (c 0.97, EtOAc). Similarly (-)-**4** (160 mg, 0.7 mmol), gave (+)-**5** (145 mg, 85%); $[\alpha]_D^{21}$ = + 71.6 (c 1.1, EtOAc).[10]

Reduction of (+)-5 into (-)-4

A mixture of optically active (+)-**5** (23 mg, 0.1 mmol), 1 mL of water, 0.15 mL of concentrated hydrochloric acid and 65 mg of zinc powder were refluxed under vigorous stirring until the orange color of the nitroxide has disappeared (1 h). After cooling, the reaction medium was made alkaline (pH > 10) by addition of a

saturated solution of Na_2CO_3 and then extracted with ether. The combined extracts were dried over Na_2SO_4, the solvent was removed under reduced pressure, affording (-)-**4** (20 mg, 93%); ee > 98%;[9] $[\alpha]_D^{21}$ = - 17.0 (c 1.5, EtOAc).

References and notes.

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7. Relative configurations of the diastereomers have been determined by ^{1}H NMR observing the signals of their benzylic protons : they appear as a singlet in the case of the *meso* compound, as they are enantiotopic. In the case of the (±) compound they appear as an AB quartet, being diastereotopic.

8. Substantial amounts of **2b** remained at the end of the reaction if the metallation step was performed at lower temperatures or for a shorter period.

9. The enantiomeric purity of amine **4** has been estimated by ^{1}H NMR at 250 MHz, adding 1 eq of (R)-(+)-α-methoxy-α-(trifluoromethyl) phenylacetic acid (Mosher's acid) to a diluted solution of **4** in $CDCl_3$. Effective splitting of the methyl esters singlet at 3.73 ppm was observed with racemic **4**.

10. Direct determinations of enantiomeric purity of nitroxide **5** have failed so far. It was thus reduced back to amine **4** (Zn, HCl aq).[1c] Recovered **4** had an unchanged enantiomeric purity.

11. We have routinely used LDA solutions prepared from diisopropylamine, isoprene and metallic lithium in THF under ultrasonic irradiation, standardized immediately before use, see : De Nicola, A.; Einhorn, J.; Luche, J.L. *J. Chem. Res.* (S), **1991**, 278.

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