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Synthesis of Enantiopure 2,7-Diaryl-1,6-dioxaspiro[4.4]nonanes *via* Enantioselective Reduction of Prochiral γ-Nitroketones by Diisopinocampheylchloroborane (DIP-Cl™).

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Abstract: The enantioselective reduction of γ-nitroketones **1-4** and γ-nitrodiketones **5-6** by the chiral reducing agent (+)- or (-)-diisopinocampheylchloroborane (DIP-Cl™) afforded respectively nitroalcohols **7-9** with e.e.'s ranging from 33 to 86% and nitrodiols **11-12** with complete diastereoselectivity and e.e. > 95 %. Nitrodiols (1*S*,7*S*)-**11** and (1*S*,7*S*)-**12** were then used as chiral precursors for the synthesis of the enantiopure 2,7-diphenyl- and 2,7-di-(2'-methoxyphenyl)-2,6-dioxaspiro[4.4]nonanes, **21** and **22**, as EE/ZZ mixtures.

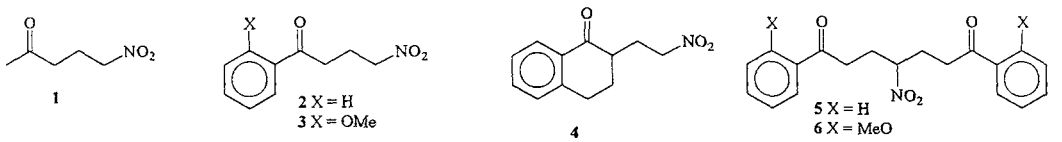
The presence of different spiroacetal moieties in many natural products such as pheromones, marine and fungal toxins, pesticides, ionophore compounds and polyether antibiotics has led during the last decades to several efforts aimed to find general synthetic strategies for these structures.[1] We have recently undertaken a study directed toward the synthesis of enantiomerically pure spiroacetal compounds, focusing on the synthesis of 2,7-disubstituted 1,6-dioxaspiro[4.4]nonanes. So far, most of work appeared in literature has concerned the synthesis of these spiroacetals having alkyl substituents because of their occurrence in nature as pheromones.[1] To the best of our knowledge, only one synthesis of racemic 2,7-diaryl substituted 1,6-dioxaspiro[4.4]nonanes was undertaken,[1e] and no studies on their biological properties were made. Moreover, enantiopure 2,7-diaryl substituted spiroacetals bearing chelating groups on the aromatic rings as **22** are a new type of compound which could have interesting ligand properties towards cations and could be used as external chiral ligands in asymmetric synthesis.[2]

Recently we have reported the high diastereo- and enantioselective baker's yeast reduction of 5-nitro-2,8-nonanedione which afforded the enantiopure 5-nitro-2,8-nonanediol with (2*S*,8*S*) absolute configuration. This was then used as a precursor for the synthesis based on the Nef reaction of enantiopure 2,7-dimethyl-1,6-dioxaspiro[4.4.]nonanes.[3] Therefore we decided to extend the same methodology to the synthesis of 2,7-diaryl substituted spiroacetals.

However, with baker's yeast reductions some compounds are not accepted as substrates and furthermore there is no way to control the stereochemical outcome of the reactions. These are perhaps the main limits of such transformations. For these reasons, and also because of a more general interest in nitroalcohols as chiral precursors for the synthesis of heterocyclic compounds,[4] we investigated the enantioselective

transformation of nitroketones to nitroalcohols by other means, i.e. the hydrogenation with chiral homogeneous catalysts[5] and, reported herein, the reduction by the chiral reagent (+)- or (-)-diisopinocampheylchloroborane (DIP-Cl™). This chiral reducing reagent, commercially available in both enantiomers, reduces arylketones usually with high enantiomeric excesses and predictable stereochemistry, and it is reported to be compatible with the nitro group.[6] Therefore, we reduced with (+)- and (-)-diisopinocampheylchloroborane different γ-nitroketones and nitrodiketones (Figure 1); among these compounds, **1-3**[4] and **4** had previously been submitted to microbial reduction.

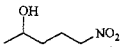
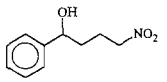
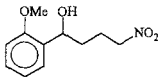
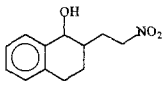
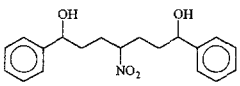
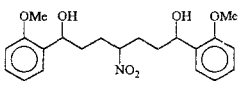
Figure 1. Substrates submitted to reduction with DIP-Cl.



Nitroketones **1-4** were prepared by conjugate addition of nitromethane to the appropriate Mannich base or vinylketone as reported.[4] Nitrodiketones **5-6** were prepared by conjugate addition of nitroketones **2-3** to the corresponding vinylketones **17** and **18** in 44-51% yield without solvent and in presence of Amberlyst A21 as shown in Scheme 1. Aryl vinyl ketones **17-18** were obtained by treating salts **15-16**, prepared from Mannich bases **13-14**,[4] with KOH in a Et_2O/H_2O two phase system and in 30-49% overall yields. The reductions with (+)- or (-)-DIP-Cl (see Table 1) were carried out at -25 °C in THF or CH_2Cl_2. For nitrodiketones **5** and **6** this choice is dependent on the solubility of the substrate.

Unsatisfactory results were obtained with aliphatic nitrocompound **1** which was converted to alcohol (*S*)-**7** by (+)-DIP-Cl in THF and (*R*)-**7** by (-)-DIP-Cl in CH_2Cl_2 in both cases with low e.e.'s (33 and 35%). Absolute configurations and enantiomeric purities were evaluated by ^{1}H-NMR analysis of Mosher ester derivatives of **7** as reported.[4,7] Even though the conversion to nitroalcohol was complete, the low yields of reaction (18-28%) were due to some difficulties encountered in the purification by chromatography. Indeed, the procedure used by us for the work-up (evaporation of α-pinene under vacuum and treatment with diethanolamine of the residue in diethyl ether) always leaves in the final mixture some unreacted DIP-Cl with almost identical R_f to **7** on silica gel chromatography with eluants having different polarity. Also distillation under reduced pressure failed to give greater amount of pure nitroalcohol. Nitroketone **4** did not react at all, and even after 67 h at -25 °C in THF no alcohol **10** was detected by ^{1}H-NMR analysis of the crude reaction mixture. The steric hindrance around the carbonyl group can explain this result, also considering that tetralone itself required 50 h to be completely reduced by (-)-DIP-Cl.[6] It is interesting to notice here that compound **4** was not reduced at all also by baker's yeast.

Table 1. Reduction of γ-nitroketones 1-6 by (+)- and (-)-DIP-Cl at -25 °C to nitroalcohols 7-12.

Nitroketones	Nitroalcohols	Solvent	DIP-Cl	Time (h)	Yield (%)	Conf.	e.e. (%)	$[\alpha]^{25}_D$
1	 7	THF	(+)	6	18	*S*	33	+ 6.1
		CH_2Cl_2	(-)	6	28	*R*	35	- 6.5
2	 8	THF	(+)	6	37	*R*	76	+ 39.3
		CH_2Cl_2	(-)	5	31	*S*	76	- 39.5
3	 9	CH_2Cl_2	(+)	5	50	*R*	86	+ 24.2
4	 10	THF	(-)	67	0	-	-	-
5	 11	CH_2Cl_2	(+)	5	74	*R,R*	> 95	+ 46.7
		CH_2Cl_2	(-)	5	59	*S,S*	> 95	- 46.3
6	 12	CH_2Cl_2	(+)	5	48	*R,R*	> 95	+ 29.9
		CH_2Cl_2	(-)	5	59	*S,S*	> 95	- 31.1

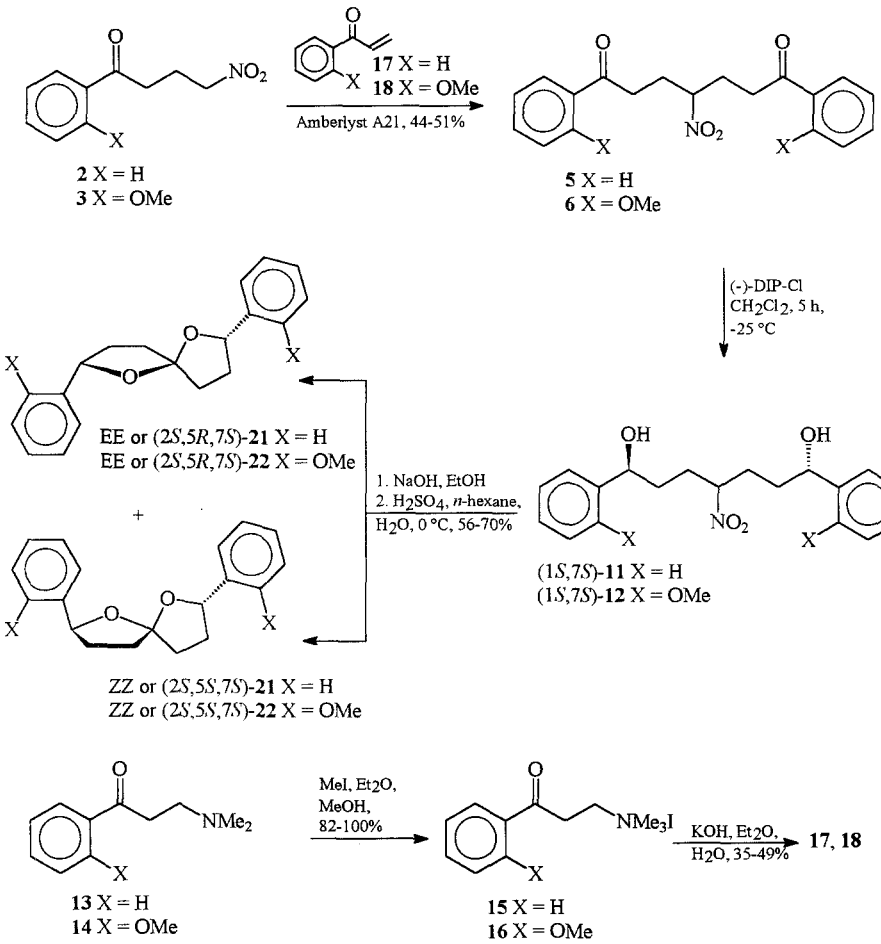
Nitroketones **2** and **3** gave after 5 h in dichloromethane nitroalcohols (*S*)-**8** (76% e.e.) and (*R*)-**9** (86% e.e.) with (-)- and (+)-DIP-Cl, respectively. For compound **2** the same result was obtained running the reaction in THF with (+)-DIP-Cl, obtaining **8** in 76% e.e. and, as expected, (*R*) absolute configuration. Also in these cases e.e.'s and absolute configurations were determined by ^{1}H-NMR analysis of their Mosher ester derivatives.[4,7] As in the reductions of **1** in dichloromethane and THF, the change in the reaction medium did not affect the enantiomeric purity of **8**. It is known that DIP-Cl can be used in both polar and non-polar aprotic solvent with only very small changes in the e.e.'s,[6] and our results are consistent with this. Conversions were in all cases complete, but the yields of **8** were strongly lowered during the purification by chromatography as described for aliphatic nitroalcohol **7**.

Finally, excellent results were obtained in the reduction of aromatic nitrodiketones **5** and **6**, which afforded enantiopure starting materials for the synthesis of spiroacetals.

The reductions were carried out in dichloromethane at -25 °C with both (+)- and (-)-DIP-Cl. The conversion of the nitrodiketones was complete (by ^{1}H-NMR analysis of the crude reaction mixtures) in 5 h and the yields, after chromatography, were fair (48-74%). For the determination of the enantiomeric excesses and absolute configurations we used both spectroscopic and chemical methods. First of all, we excluded the presence of *meso* forms by analysis of decoupled ^{13}C-NMR spectra, pointing out the complete diastereoselectivity of such DIP-Cl reductions. Indeed, the C-4 signals at 88.9 and 87.8 ppm of the *meso* forms were absent for compound **11**, as well as the C-4 signals at 89.2 and 88.1 of the *meso* forms of **12**. The signals of *meso* forms of compounds **11** and **12** were previously found by reducing with $NaBH_4$ nitrodiketones **5-6** and

then recording the spectra of the diastereomeric mixtures obtained. The absence of the *meso* forms was, as reported later, confirmed by the analysis of the diastereomeric spiroacetals mixtures obtained starting from (-)-**11** and (-)-**12**.

Scheme 1

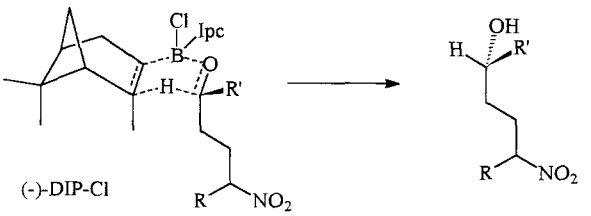


Concerning the enantiomeric purities our results are in accordance with the enantioselection observed in the reduction with DIP-Cl of aliphatic unhindered ketones[6,8] where the enantiomeric excesses are lower than 32%, and of arylalkyl ketones, such as acetophenone derivatives,[6,8] where much higher e.e.'s are always obtained. In the case of aliphatic nitroketone **1** the $-CH_2-CH_2-CH_2-NO_2$ chain apparently does not provide sufficient steric hindrance (with respect to the methyl group) to differentiate the two diastereomeric transition states and therefore a low e.e. is obtained. With the aromatic nitroketones the aryl ring seems now to become clearly the *large* group and better e.e.'s are obtained. The substitution on the phenyl ring with the *o*-MeO group

has a small effect on the enantiomeric excesses of nitroalcohol **9**, as already observed for acetophenone derivatives.[6]

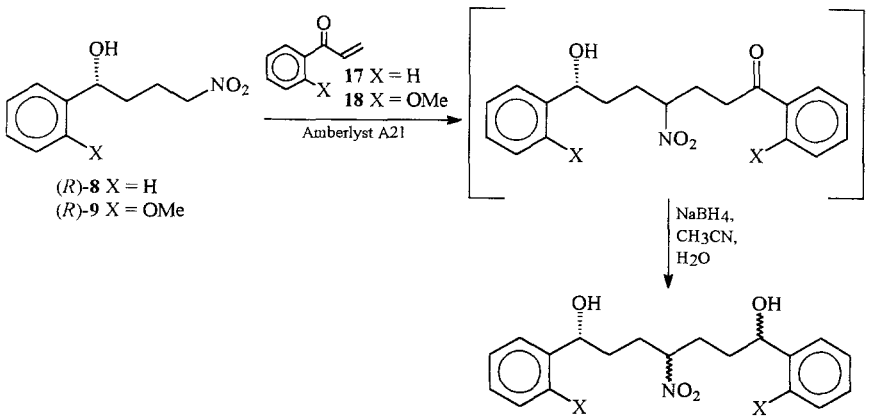
However, referring to the absolute configurations, those obtained for **7** [(*S*), with (+)-DIP-Cl; (*R*), with (-)-DIP-Cl] were unexpected on the basis of a model for the transition state,[6,8] whereas the absolute configurations of aromatic nitroalcohols **8-9** and **11-12** (see Table 1), were correctly forecasted on the basis of the same model. A possible explanation of these results is that nitroketones approach always to the borane with the -CH_2-CH_2-CHR-NO_2 nitroalkyl chain preferentially oriented in the axial direction, as reported in Figure 2.

Figure 2. Model of the transition state for the reduction of γ-nitroketones with (-)-DIP-Cl.



R' = Me, Ar
R = H, -$(CH_2)_2$-C(H)O(H)-Ar

Scheme 2



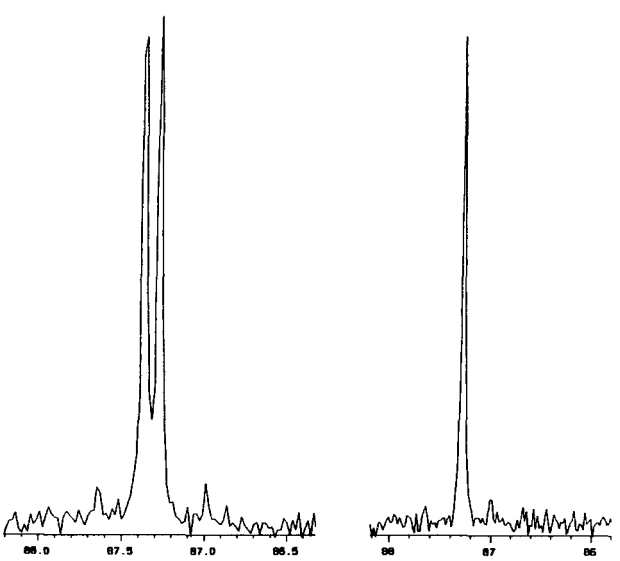
(1*R*,4*RS*,7*S*)-**19** and (1*R*,7*R*)-**11** X =H
(1*R*,4*RS*,7*S*)-**20** and (1*R*,7*R*)-**12** X = OMe

The absolute configurations of both (+)-**11** and (+)-**12** were determined by comparison of the sign of their specific rotation with that of the enantiomerically enriched (1*R*,7*R*) nitrodiols in mixture with the optically inactive (1*R*,4*RS*,7*S*) *meso* forms. These mixtures were obtained as reported in Scheme 2.

Coupling of (*R*)-**8** (76% e.e.) with vinyl ketone **17** afforded an adduct which was symmetrically reduced by $NaBH_4$. In this way a diastereomeric mixture of *meso* forms (1*R*,4*RS*,7*S*)-**19** and the (1*R*,7*R*) enantiomer was obtained presumably with the same optical purity of the starting material, which gave a value of specific rotation $[\alpha]^{25}_D = +15.1$ (*c* 2.51, $CHCl_3$). Therefore the absolute configuration of (+)-**11** was (1*R*,7*R*). The same result was achieved for (+)-**12**, starting from (*R*)-**9** (86% e.e.) as depicted in Scheme 2. Also in this case the absolute configuration of (+) enantiomer was (1*R*,7*R*), the optical rotation of the final mixture **20** and (1*R*,7*R*) compound being $[\alpha]^{25}_D = +13.0$ (*c* 1.00, $CHCl_3$) and that of (+)-**12** $[\alpha]^{25}_D = +29.9$ (*c* 0.68, $CHCl_3$).

The enantiomeric excesses of (+)- and (-)-**11** were determined by comparison of the areas of the C-4 signals in the ^{13}C-NMR spectra of their Mosher ester derivatives with those of the C-4 signals of a 1 : 1 (1*R*,7*R*) and (1*S*,7*S*) mixture prepared by mixing equal amounts of the two enantiomers (Figure 3). For (1*R*,7*R*)-(+)-**11** Mosher derivative the C-4 carbon resonates at 87.26 ppm, and for the Mosher ester derivative of its enantiomer at 87.36 ppm. The compounds appeared to be enantiopure but the sensitivity of this determination was determined by adding small amounts of (1*R*,7*R*)-**11** to a $CDCl_3$ solution of its enantiomer and recording the spectra. In this way we were able to measure an e.e. > 95% for nitrodiols **11**. In the case of (+)- and (-)-**12** the separation of the C-4 signals in the ^{13}C-NMR spectra (87.57 and 87.61 ppm) of their Mosher ester derivatives was not sufficient to determine the e.e.'s with some accuracy, but in the proton NMR spectra the *o*-methoxy group in (1*R*,7*R*)-**12** ester derivative resonated at 3.82 ppm and in (1*S*,7*S*)-**12** ester derivative at 3.78 ppm. This made it possible to assign an e.e. greater than 95% to both the enantiomers of **12**.

Figure 3. ^{13}**C-NMR signals (C-4) for Mosher esters of a (1*R*,7*R*)-11/(1*S*,7*S*)-11 (1 : 1) mixture (left) and pure (1*R*,7*R*)-11 (right).**

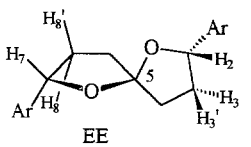


Nitrodiols (1*S*,7*S*)-(-)-**11** and (1*S*,7*S*)-(-)-**12** were converted into the target spiroacetal compounds **21** and **22** by submitting them to the conditions of the Nef reaction (Scheme 1) as reported.[3] The attack of the two hydroxy groups to the C=O double bond, generated at the C-4 position of the diols, occurs with retention of configuration of the two carbinolic stereocenters.[9] Therefore we can assign an e.e. > 95% to the diastereomeric spiroacetals **21** and **22** (which should maintain the optical purity of the starting material) and the (*S*) absolute configuration to the stereocenters at C-2 and C-7.

Spiroacetal **21** ($[\alpha]^{25}_D$ = - 93.1, *c* 0.52, $CHCl_3$) was obtained as a diastereomeric (2*S*,5*R*,7*S*)/(2*S*,5*S*,7*S*) or EE/ZZ[10] mixture in 1.25 : 1 ratio determined by ^{1}H-NMR and HPLC analyses. Spiroacetal **22** ($[\alpha]^{25}_D$ = - 76.1, *c* 0.350, $CHCl_3$) was obtained with a EE/ZZ 2.5 : 1 ratio by ^{1}H-NMR analysis of the mixture. As expected, in both cases the major compound was the thermodynamically favoured EE isomer.

Analytical HPLC and NMR spectroscopies revealed only the diastereoisomers EE and ZZ in the final mixtures and the presence of EZ isomers was therefore excluded. This confirmed the complete diastereoselectivity in the DIP-Cl reduction of aromatic nitrodiketones **5-6** already pointed out, because EZ spiroacetals, i.e. (2*S*, 5*RS*, 7*R*)-**21** and (2*S*, 5*RS*, 7*R*)-**22** derive from the cyclization of *meso* forms of the nitrodiols. The unambiguous assignment of ^{1}H- and ^{13}C-NMR signals was possible after separation of diastereoisomers EE-**21** ($[\alpha]^{25}_D$ = - 65.3, *c* 1.23, $CHCl_3$) and ZZ-**21** ($[\alpha]^{25}_D$ = - 175.4, *c* 0.65, $CHCl_3$) by preparative reverse phase HPLC, whilst the high EE/ZZ ratio for spiroacetals **22** made simpler the assignment of the NMR signals. The most significant data are reported in Table 2. The assignment of EE structure to the major diastereoisomer is based on the observation that in ^{13}C-NMR spectra the equivalent carbon atoms C-2 and C-7 underwent upfield shift in diastereoisomers EE-**21** and EE-**22** (79.7 and 74.8 ppm, respectively) with respect to diastereoisomers ZZ-**21** and ZZ-**22** (82.6 and 76.2 ppm, respectively).

Table 2. Most significant ^{1}H- and ^{13}C-NMR chemical shifts (in ppm) of 21 and 22

 EE	ZZ-21	EE-21	ZZ-22	EE-22
H-2/H-7	4.98 (t)	5.17 (t)	5.37 (t)	5.46 (t)
H-3/H-8	2.35-2.20	1.87 (m)	2.45-1.85	1.74 (m)
H-3'/H-8'	2.35-2.20	2.53 (m)	2.45-1.85	2.65 (m)
C-2/C-7	82.6 (d)	79.7 (d)	76.2 (d)	74.8 (d)
C-5	115.3 (s)	115.7 (s)	115.0 (s)	115.3 (s)

Moreover, the spiroacetal carbon C-5 was shifted upfield in ZZ-**21** and ZZ-**22** (115.3 and 115.0 ppm, respectively) with respect to EE diastereoisomers (115.7 and 115.3 ppm). These results are consistent with the

NMR data previously reported for other EE and ZZ 2,7-disubstituted 1,6-dioxaspiro[4.4]nonanes (for example for 2,7-dimethyl, 2,7-diethyl and 2,7-di-*n*-propyl spiroacetals C-2/C-7 atoms are 1.8-2.0 ppm upfield shifted in EE diastereoisomers and C-5 is 0.5 ppm downfield shifted in the EE diastereoisomers),[11,12] and we may argue that changes in the carbon chemical shifts are due to EE or ZZ configuration more than to the type of substituents at C-2 and C-7.

The ^{1}H-NMR signals of the equivalent H-2 and H-7 atoms are different for the EE and ZZ diastereoisomers. Indeed, these protons in EE-**21** and EE-**22** isomers underwent a slight downfield shift (5.17 and 5.46 ppm, respectively) with respect to the same protons in ZZ (4.98 and 5.37 ppm). Furthermore, in EE spiroacetals the aromatic ring has shielding effect on the equivalent protons H-3 and H-8, which resonate at 1.87 (compound **21**) and 1.74 ppm (compound **22**). The effect is instead of deshielding on H-3' and H-8', which resonate at 2.53 (compound **21**) and 2.65 ppm (compound **22**). The same effect was not observed in ZZ diastereoisomers and all protons resonate in a narrow region around 2 ppm.

The effect of the aromatic rings in both **21** and **22** could be explained on the basis of their different orientation in EE and ZZ isomers. This was supported by molecular modelling calculations[13] which showed that in ZZ isomers the aryl rings are facing each other, one being in the pseudoaxial position and the other in the pseudoequatorial position. In this way both H-3 and H-3' (and H-8 and H-8') undergo the same slight deshielding effect. In EE isomers the aryl rings lie in pseudoequatorial position and both in a plane almost parallel to that containing the two vicinal protons. Therefore, *cis* protons H-3 and H-8 should suffer a shielding effect by the aromatic rings whereas *trans* protons (H-3' and H-8') undergo a deshielding effect.

In conclusion, the reduction by DIP-Cl of nitroketones to chiral nitroalcohols is an effective alternative to the microbiological reductions and enzymatic methods used until now for the preparation of these important precursors in asymmetric synthesis. Both the enantiomers of the desired nitroalcohol can be obtained with this reagent, with a predictable stereochemical outcome and, especially for aromatic nitroketones, with high optical purity. The asymmetric reduction of 1,7-disubstituted 4-nitrodiketones with this reagent occurs with complete enantioselectivity affording nitrodiols with C_2 symmetry which could be of great interest as potential precursors of chiral auxiliary compounds in organic synthesis. The direct conversion of nitrodiols **11** and **12** to enantiopure spiroacetals **21** and **22** under the acidic conditions of the Nef reaction then represents a first example of their potential in asymmetric synthesis.

Experimental

Melting points were determined with a Büchi 510 apparatus. IR spectra were recorded with a Perkin Elmer 881 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ on a Varian Gemini instrument at 200 MHz. MS spectra were obtained at 70 eV with a Carlo Erba QMD 1000 spectrometer and a Hewlett Packard A-5790-5970 GC-MS instrument. Elemental analysis were performed with a Perkin Elmer

240 C and HPLC analysis with a Gilson System (UV 116 Deuterium lamp), equipped with Alltech Econosphere analytical C_{18} 5μ 250 x 4.6 and preparative C_{18} 10μ 250 x 10 columns. The R_f values refer to TLC on 0.25 mm silica gel plates (Merck F_{254}). Chromatographic purifications were performed by flash column chromatography on silica gel. Compounds **1-3**,[4] and **13-14**[4] were prepared as reported. Nitroalcohols **7-9**[4] have already been prepared and fully characterised in their racemic and enantiopure forms.

2-(2-Nitroethyl)tetralone 4. Nitrocompound **4** was prepared according to the procedure already reported for the synthesis of γ-nitroketones.[4] M.p. 45-46 °C; R_f = 0.35 (petroleum ether/ethyl acetate 4 : 1); ^{1}H-NMR δ (ppm): 8.00 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.47 (dt, *J* = 7.4, 1.6 Hz, 1 H), 7.34-7.21 (m, 2 H), 4.65 (t, *J* = 6.8 Hz, 2 H), 3.02 (t, *J* = 4.2 Hz, 2 H), 2.67-2.47 (m, 2 H), 2.28-2.18 (m, 1 H), 2.03-1.89 (m, 2 H). ^{13}C-NMR δ (ppm): 198.9 (s), 143.6 (s), 135.5 (s), 133.6 (d), 128.7 (d), 127.4 (d), 126.8 (d), 76.6 (t), 44.7 (d), 29.4 (t), 29.0 (t), 28.2 (t). IR ($CDCl_3$) 3064, 3025, 2933, 2864, 1677, 1599, 1547, 1381 cm^{-1}. MS *m/z* (%) 219 (M^+, 2), 172 (28), 171 (26), 118 (100), 115 (41), 90 (74), 89 (52).

Phenyl vinyl ketone 17. To a solution of amine **13** (18.43 g, 0.104 moles) in methanol (200 ml) was added dropwise, with cooling by an ice/water bath, MeI (9.71 ml, 0.156 moles). The solution was then left overnight under vigorous stirring at r.t. The salt formed was filtered, washed with ether and dried under vacuum, obtaining **15** (27.25 g, 82%) as a white solid (m.p 195-198 °C). Part of this salt (8.03 g, 25 mmoles) was dissolved in water (75 ml), diethyl ether (130 ml) was added and the resulting mixture cooled at 0 °C. A solution of KOH (2.81 g, 50 mmoles) in water (75 ml) was then added dropwise and the mixture was left under stirring 18 h at r.t. The organic phase was separated and the aqueous layer extracted with ether (2 x 50 ml). The organic extracts were combined and washed with 5% HCl (2 x 50 ml), brine and dried over sodium sulphate. After filtration and evaporation of the solvent, **17** (1.14 g, 35%) was obtained as a yellow oil which was quickly used to avoid its degradation. ^{1}H-NMR δ (ppm): 7.93 (m, 2 H), 7.62-7.40 (m, 3 H), 7.15 (dd, *J* = 17.2, 1.9 Hz, 1 H), 6.43 (dd, *J* = 17.2, 1.9 Hz, 1 H), 5.92 (dd, *J* = 10.6, 1.9 Hz, 1 H).

2'-Methoxyphenyl vinyl ketone 18. The same procedure reported above was used, but dissolving the amine in a Et_2O (50 ml) and MeOH (25 ml) mixture. Starting from free amine **14** (4.96 g, 23.9 mmoles), salt **16** (8.45 g, 100%) was obtained as a white solid (m.p. 130-135 °C) then trasformed into vinyl ketone **18** (1.906 g, 49%) as a yellow oil: ^{1}H-NMR δ (ppm): 7.55 (dd, *J* = 7.7, 1.8 Hz, 1 H), 7.45 (td, *J* = 7.7, 1.5 Hz, 1 H), 7.06-6.90 (m, 3 H), 6.26 (dd, *J* = 17.2, 1.1 Hz, 1 H), 5.79 (dd, *J* = 10.6, 1.1 Hz, 1 H), 3.85 (s, 3 H).

1,7-Diphenyl-4-nitroheptan-1,7-dione 5.[14] Nitroketone **2** (2.00 g, 10.36 mmoles) and vinyl ketone **17** (1.14 g, 8.63 mmoles) were mixed with cooling at 0 °C, and after 10 min Amberlyst A21 (2.56 g) was added. The mixture was left 18 h under stirring and nitrogen atmosphere, then extracted with CH_3CN (4 x 30 ml) and dried over sodium sulphate. After evaporation of the solvent, the crude oil was chromatographed (dichloromethane) obtaining **5** (1.23 g, 44%) as a white solid. R_f = 0.4; ^{1}H-NMR δ (ppm): 7.91 (m, 4 H), 7.80-7.35 (m, 6 H), 4.76 (m, 1 H), 3.05 (t, *J* = 7.0 Hz, 4 H), 2.35 (m, 4 H); MS *m/z* (%): 279 (M^+-46, 3), 278 (4), 159 (7), 106 (10), 105 (100), 77 (77).

1,7-Di-(2'-methoxyphenyl)-4-nitroheptan-1,7-dione 6. The same procedure reported above was used. Starting from nitroketone **3** (2.24g, 9.81 mmoles) and vinyl ketone **18** (1.33 g, 8.18 mmoles), pure **6** (1.60 g, 51%) was obtained after chromatography (dichloromethane) as a white solid: m.p. 53-55 °C; R_f = 0.4; ^{1}H-NMR δ (ppm): 7.70 (m, 2 H), 7.45 (m, 2 H), 7.02-6.88 (m, 4 H), 4.70 (m, 1 H), 3.88 (s, 6 H), 3.05 (t, *J* = 7.0 Hz, 4 H), 2.30 (m, 4 H). ^{13}C-NMR δ (ppm): 200.0 (s, 2 C), 158.7 (s, 2 C), 134.9 (d, 2 C), 130.4 (d, 2 C), 127.4 (s, 2 C), 120.7 (d, 2 C), 11. 5 (d, 2 C), 87.7 (d, 1 C), 55.5 (q, 2 C), 39.6 (t, 2 C), 28.4 (t, 2 C). IR ($CDCl_3$) 1670, 1595, 1545, 1482, 1435, 1284, 1243 cm^{-1}; MS *m/z* (%): 385 (M+, 0.2), 136 ((), 135 (100), 77 (14). Elemental analysis calcd for $C_{21}H_{23}NO_6$: C, 65.43; H, 6.01; N, 3.65. Found: C, 65.18; H, 6.19; N, 3.68.

***(R)*-(-)-5-Nitropentan-2-ol 7**. In a dry-flamed three necked flask, equipped with a thermometer, (-)-DIP-Cl (1.47 g, 4.58 mmoles) was dissolved in anhydrous dichlorometane (10 ml) under nitrogen atmosphere and magnetic stirring. The solution was cooled at - 25 °C and a solution of nitroketone **1** (500 mg, 3.81 mmoles) in dichloromethane (10 ml) was slowly added by a syringe. The solution was left at - 25 °C for 6 h, then the solvent was evaporated and the α-pinene formed during the reaction removed under high vacuum (1,5 x 10^{-1} mbar) for 8 h. The residue was then treated with diethanolamine (730 µl, 7.62 mmoles) in Et_2O (15 ml) for 2 h, the solid formed filtered off and the solvent removed to give a crude oil which was chromatographed (dichloromethane) obtaining **7** (140 mg, 28%) as a colourless oil: R_f = 0.1; $[\alpha]^{25}_D$ = - 6.5 (*c* 0.57, $CHCl_3$).

(S)-(+)-5-Nitropentan-2-ol 7. Procedure as reported above but in THF as solvent. Starting from **1** (2 g, 15 mmoles), (*S*)-(+)-**7** was obtained (367 mg, 18%): $[\alpha]^{25}_D$ = + 6.1 (*c* 0.61, $CHCl_3$).

(S)-(-)-1-Phenyl-4-nitrobutanol 8. Procedure as reported for reduction of **1** in CH_2Cl_2, reaction time 5 h. Starting from **2** (1.00 g, 5.18 mmoles) after chromatography (dichloromethane) (*S*)-(-)-**8** (317 mg, 31%) was obtained as a yellow oil: R_f = 0.15; $[\alpha]^{25}_D$ = - 39.5 (*c* 0.81, $CHCl_3$).

(R)-(+)-1-Phenyl-4-nitrobutanol 8. Procedure as reported for reduction of **1** but in THF as solvent. Starting from **2** (1.1 g, 5.7 mmoles) (*R*)-(+)-**8** (397 mg, 37%) was obtained: $[\alpha]^{25}_D$ = + 39.3 (*c* 0.69, $CHCl_3$).

(R)-(+)-1-(2'-Methoxyphenyl)-4-nitrobutanol 9. Procedure as reported for reduction of **1** in CH_2Cl_2, reaction time 5 h. Starting from **3** (1.00 g, 4.48 mmoles) after chromatography (dichloromethane) (*R*)-(+)-**9** (504 mg, 50%) was obtained: R_f = 0.15; $[\alpha]^{25}_D$ = + 24.2 (*c* 0.88, $CHCl_3$).

(1*S*,7*S*)-(-)-1,7-Diphenyl-4-nitroheptan-1,7-diol 11. In a dry-flamed three necked flask, equipped with a thermometer, (-)-DIP-Cl (1.45 g, 4.52 mmoles) was dissolved in anhydrous dichlorometane (8 ml) under nitrogen atmosphere and magnetic stirring. The solution was cooled at - 25 °C and a solution of the nitrodiketone **5** (656 mg, 2.02 mmoles) in dichloromethane (4 ml) was slowly added by a syringe. The solution was left at - 25 °C for 5 h, then the solvent was evaporated and the α-pinene formed during the reaction removed under high vacuum (1,5 x 10^{-1} mbar) heating with a water bath at 50-60 °C for 8 h. The residue was then treated with diethanolamine (929 µl, 9.70 mmoles) in Et_2O (15 ml) for two hours, the solid formed filtered off and the solvent removed to give a crude oil. This was chromatographed eluting first with dichloromethane to remove unreacted material and by-products and then with dichloromethane/methanol 20 : 1 to recover

nitrodiol **11** (393 mg, 59%) as yellowish oil. $[\alpha]^{25}_D$ = - 46.3 (*c*, 0.61, $CHCl_3$); R_f = 0.2; ^{1}H-NMR δ (ppm): 7.40-7.20 (m, 10 H), 4.66 (m, 2 H), 4.54 (m, 1 H), 2.10-1.65 (m, 10 H). ^{13}C-NMR δ (ppm): 143.9 (s, 2 C), 128.5 (d, 4 C), 127.7 (d, 2 C), 125.6 (d, 4 C), 88.4 (d, 1 C), 73.5 (d, 1 C), 72.9 (d, 1 C), 34.9 (t, 1 C), 34.6 (t, 1 C), 30.2 (t, 1 C), 29.9 (t, 1 C); IR ($CDCl_3$) 3607, 3375 (br), 3065, 3031, 2936, 1543, 1492, 1445, 1369, 1310, 1282, 1214, 1041 cm^{-1}; MS *m/z* (%): 176 (M^+-153, 55), 174 (100), 118 (58), 117 (94), 105 (35), 104 (79), 91 (35), 77 (32); Elemental analysis calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 68.63; H, 7.40; N, 3.90.

(1*R*,7*R*)-(+)-1,7-Diphenyl-4-nitroheptan-1,7-diol 11. Procedure as reported above. Starting from **5** (651 mg, 2.00 mmoles) (1*R*,7*R*)-**11** (486 mg, 74%) was obtained: $[\alpha]^{25}_D$ = + 46.7 (*c* 0.71, $CHCl_3$).

(1*R*,7*R*)-(+)-1,7-Di-(2'-methoxyphenyl)-4-nitroheptan-1,7-diol 12. Procedure as reported for reduction of **5**. Starting from **6** (901 mg, 2.34 mmoles) after chromatography (dichloromethane, then dichloromethane/methanol 20 : 1) (1*R*,7*R*)-**12** (435 mg, 48%) was obtained: R_f = 0.25 (dichloromethane/methanol 20 : 1); $[\alpha]^{25}_D$ = + 29.9 (*c* 0.68, $CHCl_3$); ^{1}H-NMR δ (ppm): 7.20 (m, 4 H), 7.00-6.75 (m, 4 H), 4.83 (m, 2 H), 4.55 (m, 1 H), 3.81 (s, 6 H), 2.60-2.35 (s br, 2 H), 2.20-1.60 (m, 8 H); ^{13}C-NMR δ (ppm): 156.4 (s, 2 C), 131.5 (s, 2 C), 128.6 (d, 2 C), 126.7 (d, 2 C), 120.8 (d, 2 C), 110.5 (d, 2 C), 88.7 (d, 1 C), 70.5 (d, 1 C), 70.0 (d, 1 C), 55.3 (q, 2 C), 33.2 (t, 1 C), 33.0 (t, 1 C), 30.7 (t, 1 C), 30.3 (t, 1 C); IR ($CDCl_3$): 3609, 3003, 2935, 1546, 1488, 1237 cm^{-1}; MS *m/z* (%): 235 (M^+-154, 4), 137 (100), 135 (79), 121 (70), 107 (74), 91 (50), 77 (57); Elemental analysis calcd for $C_{21}H_{27}NO_6$: C, 64.76; H, 6.99; N, 3.60. Found: C, 64.42; H, 7.02; N, 3.89.

(1*S*,7*S*)-(-)-1,7-Di-(2'-methoxyphenyl)-4-nitroheptan-1,7-diol 12. Procedure as above. Starting from **6** (761 mg, 1.97 mmoles) (1*S*,7*S*)-**12** (455 mg, 59%) was obtained: $[\alpha]^{25}_D$ = - 31.1 (*c* 0.38, $CHCl_3$).

(2*S*,5*R*,7*S*)-(-)- and (2*S*,5*S*,7*S*)-(-)-2,7-Diphenyl-1,6-dioxaspiro[4.4]nonanes 21. A solution of nitrodiol (1*S*,7*S*)-**11** (353 mg, 1.07 mmoles) in absolute ethanol (9 ml) was added dropwise to a solution of sodium hydroxide (172 mg, 4.28 mmoles) in 5 ml of ethanol, under nitrogen at room temperature. After 10 min stirring, the solvent was evaporated and the resulting salt dissolved in water (10 ml). This solution was slowly added to a two-layer mixture of diluted sulfuric acid (1 ml of concentrated sulfuric acid and 10 ml of water) and *n*-hexane (10 ml) under stirring and with cooling at 0 °C for 1h. The mixture was then left under stirring for 12 h at room temperature, then the organic phase was separated and the aqueous layer extracted with diethyl ether (2 x 15 ml). The combined organic phases are washed with brine (15 ml) and dried over sodium sulfate. After evaporation of the solvent the oily residue was purified by bulb to bulb (T 200-250 °C, p 2 x 10^{-1} mbar) distillation, obtaining **21** (168 mg, 56%) as a 1.25 : 1 (2*S*,5*R*,7*S*)/(2*S*,5*S*,7*S*) diastereomeric mixture: $[\alpha]^{25}_D$ = - 93.1 (*c* 0.52, $CHCl_3$). This mixture was separated by preparative HPLC (acetonitrile/water gradient from 45 to 90% of acetonitrile in 30', 1 ml/min) affording analytically pure (2*S*,5*R*,7*S*)-**21** (94 mg, 31%) and (2*S*,5*S*,7*S*)-**21** (74 mg, 25%).

(2*S*,5*R*,7*S*)-21. Colourless oil; $[\alpha]^{25}_D$ = -65.3 (*c* 1.23, $CHCl_3$); ^{1}H-NMR δ (ppm): 7.40-7.20 (m, 10 H), 5.17 (t, *J* = 7.2 Hz, 2 H), 2.65-2.40 (m, 2 H), 2.40-2.00 (m, 4 H), 1.95-1.78 (m, 2 H); ^{13}C-NMR δ (ppm): 142.8 (s, 2 C), 128.3 (d, 4 C), 127.3 (d, 2 C), 125.8 (d, 4 C), 115.7 (s, 1 C), 79.7 (d, 2 C), 35.2 (t, 2 C), 33.8 (t, 2 C); IR ($CDCl_3$): 3087, 3065, 3030, 2981, 2947, 2879, 1601, 1491, 1448, 1366, 1338, 1279, 1212, 1198, 1134 cm^{-1}; MS *m/z* (%): 280 (M^+, 0.3), 174 (100), 118 (51), 117 (77), 104 (64), 91 (27), 77 (25); Elemental analysis calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.19; H, 7.59.

(2*S*,5*S*,7*S*)-21. Colourless oil; $[\alpha]^{25}_D$ = -175.4 (*c* 0.65, $CHCl_3$); ^{1}H-NMR δ (ppm): 7.46 (m, 4 H), 7.35-7.20 (m, 6 H), 4.98 (t, *J* = 7.5 Hz, 2 H), 2.35-2.00 (m, 8 H); ^{13}C-NMR δ (ppm): 143.0 (s, 2 C), 128.1 (d, 4 C), 127.4 (d, 2 C), 126.9 (d, 4 C), 115.3 (s, 1 C), 82.6 (d, 2 C), 37.2 (t, 2 C), 34.9 (t, 2 C); IR ($CDCl_3$): 3087, 3065, 3030, 2981, 2947, 2879, 1601, 1491, 1448, 1366, 1338, 1279, 1212, 1198, 1134 cm^{-1}; MS *m/z* (%): 280 (M^+, 1), 174 (93), 118 (76), 117 (100), 104 (81), 91 (34), 77 (31); Elemental analysis calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.27; H, 7.32.

(2*S*,5*R*,7*S*)-(-)- and (2*S*,5*S*,7*S*)-(-)-2,7-Di-(2'-Methoxyphenyl)-1,6-dioxaspiro[4.4]nonanes 22. Prepared as reported above. Starting from (1*S*,7*S*)-**12** (341 mg, 0.88 mmoles) after chromatography (dichloromethane) **22** (208 mg, 70%) was obtained as a colourless oil and 2.5 : 1 (2*S*,5*R*,7*S*)/(2*S*,5*S*,7*S*) diastereomeric mixture: $[\alpha]^{25}_D$ = - 76.1 (*c* 0.35, $CHCl_3$); IR ($CDCl_3$): 3034, 2935, 2873, 2837, 1598, 1587, 1486, 1455, 1436, 1281, 1240 cm^{-1}; MS *m/z* (%): 340 (M^+, 7), 204 (76), 147 (98), 134 (100), 119 (56), 105 (19), 91 (64), 77 (32). **(2*S*,5*R*,7*S*)-22**. ^{1}H-NMR δ (ppm): 7.40 (m, 2 H), 7.20 (m, 2 H), 7.00-6.95 (m, 4 H), 5.46 (t, *J* = 6.7 Hz, 2 H), 3.79 (s, 6 H), 2.70-2.60 (m, 2 H), 2.45-1.85 (m, 4 H), 1.80-1.65 (m, 2 H); ^{13}C-NMR δ (ppm): 156.1 (s, 2 C), 131.9 (s, 2 C), 127.7 (d, 2 C), 125.7 (d, 2 C), 120.3 (d, 2 C), 115.2 (s, 1 C), 110.1 (d, 2 C), 74.8 (d, 2 C), 55.2 (q, 2 C), 34.7 (t, 2 C), 32.4 (t, 2 C). **(2*S*,5*S*,7*S*)-22**. ^{1}H-NMR δ (ppm): 7.80 (m, 2 H), 7.20 (m, 2 H), 7.00-6.95 (m, 4 H), 5.37 (dd, *J* = 8.8, 6.2 Hz, 2 H), 3.80 (s, 6 H), 2.45-1.85 (m, 8 H); ^{13}C-NMR δ (ppm): 156.1 (s, 2 C), 131.9 (s, 2 C), 127.6 (d, 2 C), 127.3 (d, 2 C), 120.6 (d, 2 C), 115.2 (s, 1 C), 109.8 (d, 2 C), 76.2 (d, 2 C), 55.2 (q, 2 C), 37.2 (t, 2 C), 33.1 (t, 2 C). Elemental analysis calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 73.68; H, 7.48.

(1*R*,4*RS*,7*S*)-19 and (1*R*,7*R*)-(+)-11. Nitroalcohol (*R*)-**8** (2.56 g, 13.1 mmoles) and vinylketone **17** (1.72 g, 13.0 mmoles) were mixed with cooling at 0 °C, and after 10 min Amberlyst A21 (2.80 g) was added. The mixture was left 18 h under stirring and nitrogen atmosphere, then extracted with CH_3CN (3 x 20 ml), water (34 ml) was added to the combined organic extracts and the resulting solution cooled at 0 °C was treated with $NaBH_4$ (0.995 g, 26 mmoles). After 18 h stirring saturated NH_4Cl aqueous solution was added up to pH 7, the acetonitrile was rotoevaporated and the resulting aqueous solution extracted with Et_2O (4 x 30 ml). The combined organic layers were dried over sodium sulfate, filtered and evaporated affording a yellow oil. This was chromatographed (CH_2Cl_2/MeOH, 20 : 1) yielding the title compound (1.789 g, 42%) as a pale yellow oil: $[\alpha]^{25}_D$ = + 15.1 (*c* 2.51, $CHCl_3$). ^{13}C-NMR δ (ppm): 143.9 (s, 2 C), 128.5 (d, 4 C), 127.7 (d, 2 C), 125.6 (d, 4

C), 88.9 (d, *meso*), 88.4 (d), 87.8 (d, *meso*) 73.5 (d, 1 C), 72.9 (d, 1 C), 34.9 (t, 1 C), 34.6 (t, 1 C), 30.2 (t, 1 C), 30.1 (t, *meso*), 29.9 (t, 1 C), 29.6 (t, *meso*).

(1*R*,4*RS*,7*S*)-20 and (1*R*,7*R*)-(+)-12. Prepared as reported above. Starting from (*R*)-(+)-**9** (266 mg, 1.18 mmoles) and **18** (160 mg, 0.98 mmoles), after $NaBH_4$ reduction of the intermediate product and chromatography (CH_2Cl_2/MeOH, 20 : 1), title compound (189 mg, 50%) was obtained: $[\alpha]^{25}_D$ = + 13.0 (*c* 1.00, $CHCl_3$). ^{13}C-NMR δ (ppm): 156.4 (s, 2 C), 131.5 (s, 2 C), 128.6 (d, 2 C), 126.7 (d, 2 C), 120.8 (d, 2 C), 110.5 (d, 2 C), 89.2 (d, *meso*), 88.7 (d, 1 C), 88.1(d, *meso*), 70.5 (d, 1 C), 70.0 (d, 1 C), 55.3 (q, 2 C), 33.2 (t, 1 C), 33.0 (t, 1 C), 30.7 (t, 1 C), 30.5 (t, *meso*), 30.3 (t, 1 C), 30.0 (t, *meso*).

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