Pergamon

Tetrahedron, Vol. 52, No. 43, pp. 13649-13654, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00817-4

A Stereodivergent Synthesis of Chiral 4,5-Disubstituted Bis(Oxazolines).

Giovanni Desimoni,* Giuseppe Faita, and Mariella Mella.

Dipartimento di Chimica Organica, Università di Pavia, V.le Taramelli 10, 27100 Pavia, Italy.

Abstract. Bis(oxazolines), disubstituted in the 4 and 5 positions, are synthesized from dimethylmalonyl bis-diamides of the suitable 1,2-disubstituted chiral aminoethanol. Starting from the same diamide, the ring closure can be realized either with retention (reflux in xylene with dibutyl tin dichloride - the Masamune protocol) or inversion (conversion into the mesylate and reflux with aqueous ethanolic NaOH) of the configuration at the chiral center in position 5. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Chiral (2,2'-bisoxazolino)alkanes proveed to be useful ligands for the preparation of catalysts for enantioselective cyclopropanations,[1] allylic nucleophilic substitutions,[2] hydrosilylation,[3] aziridinations.[4] Extensive applications to asymmetric Diels-Alder[5] and Hetero Diels-Alder[6] reactions derived from the excellent stereo- and enantioselectivity obtained by changing either the cationic core, or the counter ion of this, or, most important, the substituents on the oxalinic ligand of the catalyst.

To infer the factors determinant in organizing ligands and reagents around the cation in a supramolecular device enantiotopically oriented, substituents with a given configuration are required not only in the position 4 of the oxazoline ring, but also in 5.

RESULTS AND DISCUSSION

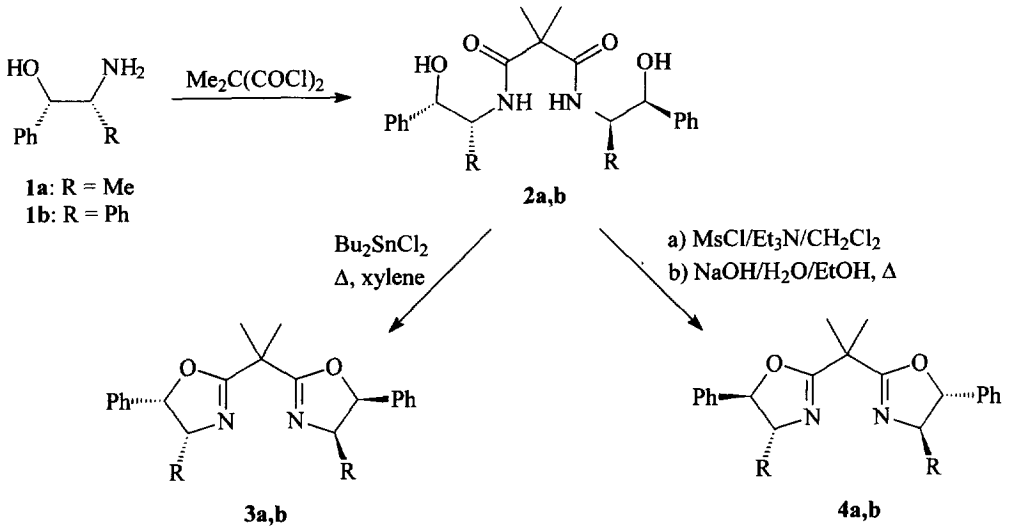
The few examples known of 4,5-disubstituted chiral bis-oxazolines, mainly with a *cis* configuration,[7,8] rarely with the *trans* one,[9] always have the configuration transmitted, as it is, from the starting amino-alcohol into the oxazoline ring.

We have developed a stereodivergent synthesis of 2,3-bis{2-[4(*R*),5(*S*) disubstituted or [4(*R*),5(*R*)-disubstituted 1,3-oxazolinyl]}propanes whose limit seems to be the availability of the disubstituted aminoethanol incorporating the chiral centers.

Commercially available (1*S*,2*R*)-norephedrine **1a**[10] or (1*S*,2*R*)-diphenylaminoethanol **1b** were made to react with dimethyl malonyl dichloride[11] and the diamides **2a,b** were obtained with excellent yields. These were the starting products of the stereodivergent syntheses of **3a,b** and **4a,b** (Scheme 1).

The 4(*R*),5(*S*)-diphenyl oxazoline **3b** was a patented product[7b] and it was obtained through the same approach. Following the Masamune protocol (reflux in xylene with dibutyl tin dichloride) the 4(*R*)-methyl-5(*S*)-phenyl dioxazoline **3a** was prepared in a 70% yield after a prolonged heating of the reaction mixture.

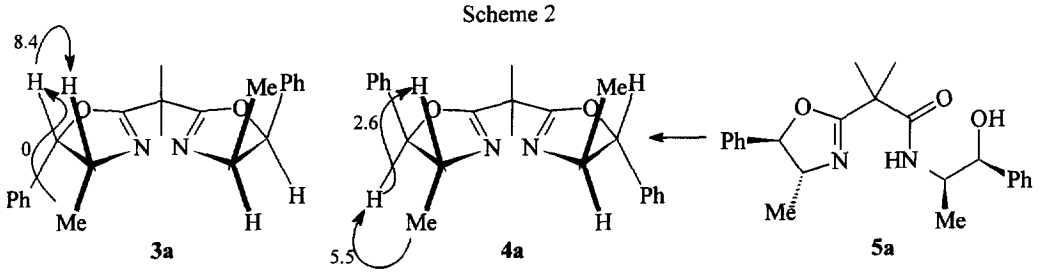
Scheme 1



The same diamides **2a,b** are the starting products of the 4(*R*),5(*R*) isomers. Methanesulfonyl chloride converted the amides into their bis-mesylate derivatives, whose ring closure with inversion of configuration at the 5,5'-centers was accomplished by heating these intermediates with aqueous ethanolic NaOH. This procedure is essentially that described by Denmark and co-workers[12] to synthesize 5-unsubstituted chiral bisoxazolines.

Through this method **4a** and **4b** were obtained in good yields, uncontamined by their *cis* isomers. Only one side product was sometimes isolated from the reaction mixture. This was the monocyclized product **5a** that, separated by column chromatography from **4a** and identified, was later converted into the same **4a** (Scheme 2). Due to the close similarity of the H_4H_5 coupling constant in *cis* and *trans* derivatives, the configuration of **3a,b** and **4a,b** was confirmed with n.O.e. experiments. The irradiation of H_4 gave a 12% enhancement of H_5 in **3b**, but 0% in **4b**. The results of the irradiation of the methyl group and of H_5 in **3a** and **4a** are shown in Scheme 2.

Scheme 2



In order to discuss the optical purity of the products, **3a,b** and **4a,b** proved to be diastereomerically pure within the limit of their ^{1}H-Nmr spectra. Thus, any racemization of the starting materials can be excluded since **1a,b** have two chiral centers and two aminoalcohol molecules are incorporated in each bis(oxazoline).

In conclusion, the great advantage of the stereodivergent synthesis described above is that a single disubstituted diamide is prepared and if this has the 1(*R*),2(*S*) configuration, as **2a,b** have, it can be converted cleanly and with good yields either into the 4(*R*),5(*S*) or the 4(*R*),5(*R*) bis(oxazolines).

EXPERIMENTAL SECTION

Melting points were determined by the capillary method and are uncorrected. Elemental analyses were performed on C. Erba CHN analyzer mod. 1106. ^{1}H-Nmr ($CDCl_3$, TMS as standard) were recorded on a Bruker AC 300 spectrometer; i.r. spectra (nujol mulls) on a Perkin Elmer 881 spectrophotometer; optical rotations at room temperature on a Perkin Elmer 241 polarimeter with a 1 dm cell. Column chromatography: silica gel 230-400 mesh.

Material - (1*S*,2*R*)-Norephedrine (**1a**) was the Aldrich 99% purity hydrochloride product, and (1*S*,2*R*)-2-amino-1,2-diphenylethanol (**1b**) was the Aldrich 99% purity product.

*N,N'-Bis[(1R)-methyl-(2S)-phenyl-2-hydroxyethyl]-2,2-dimethylpropane-1,3-diamide (**2a**).* (1*S*,2*R*)-Norephedrine hydrochloride (4.13 g - 22 mmol) was suspended in dichloromethane (30 mL) and triethylamine (4.44 g - 44 mmol) in dichloromethane (10 mL) was added dropwise under stirring, keeping the temperature below 0 °C. Stirring was continued for an additional hour, then dimethyl malonyl dichloride[11] (1.86 g - 11 mmol) in dichloromethane was added, again keeping the temperature below 0 °C. Stirring was continued overnight at room temperature, then the reaction mixture was decomposed with water. The inorganic layer was separated and the mother liquors extracted with dichloromethane. Evaporation of the solvent gave a quantitative yield of **2a**, crystallized from ethyl acetate (3.8 g - 87% yield), m.p. 147-8 °C. I.r.: $\nu_{OH,NH}$ = 3410, 3380, and 3310 cm^{-1}; ν_{CO} = 1655 and 1632 cm^{-1}. ^{1}H-Nmr, δ: 7.2-7.4 (5H, aromatic protons), 6.58 (1H, d, *J* = 10 Hz, NH), 4.90 (1H, d, *J* = 3 Hz, H_2), 4.31 (1H, m, H_1), 1.43 (3H, s, Me), 0.99 (3H, d, *J* = 7 Hz, Me). Elem. anal.: calc. for $C_{23}H_{30}N_2O_4$: C, 69.3; H, 7.6; N, 7.0. Found: C, 69.5; H, 7.7; N, 7.1%. $[\alpha]_D$ = + 61.9° (c = 0.67, chloroform).

*N,N'-Bis[(1R,2S)-diphenyl-2-hydroxyethyl]-2,2-dimethylpropane-1,3-diamide (**2b**).* This was prepared following the method described in the literature[7b] from (1*S*,2*R*)-2-amino-1,2-diphenylethanol (2.5 g - 12 mmol), triethylamine (3.0 g - 30 mmol) in dichloromethane (25 mL). Dimethyl malonyl dichloride[11] (1.0 g - 6 mmol) in dichloromethane (5 mL) was added dropwise under N_2, keeping the temperature below 0 °C. Stirring was continued overnight at room temperature, then the reaction mixture was decomposed with H_2O. A white solid separated that was filtered after evaporation of the dichloromethane. Washing with HCl 1*N* gave **2a** (3.0 g - 98% yield) crystallized from ethyl acetate, m.p.200-1 °C (lit.[7b] 180-2 °C). I.r.: $\nu_{OH,NH}$ = 3415 and 3390 cm^{-1}; ν_{CO} = 1655 and 1643 cm^{-1}. ^{1}H-Nmr: two conformers (ratio 47:53) one H-bonded between NH

and OH, one not bonded; δ: 6.9-7.3 (10H, aromatic protons); conformer not H-bonded: 7.31 (1H, d, J = 8 Hz, NH), 5.24 (1H, dd, J = 8 and 4.4 Hz, H_1, irradiation at 7.31 gave a doublet, J = 4.4 Hz), 5.05 (1H, d, J = 4.4 Hz, H_2), 1.37 (3H, s, Me); conformer H-bonded: 9.7 (1H, broad adsorption, NH), 3.10 (1H, dd, J = 7.2 and 4.8 Hz) and 3.05 (1H, dd, J = 4.3 and 7.2 Hz) (H_1 and H_2, irradiation at 9.7 δ gave an AB system with J = 7.2 Hz), 1.41 (3H, s, Me). $[\alpha]_D$ = + 22.2° (c = 0.49, chloroform).

*2,2-Bis{2-[4(R)-methyl-5(S)-phenyl-1,3-oxazolinyl]}propane (**3a**).* Bis-amide **2a** (0.8 g - 2 mmol), dissolved in anhhydrous xylene (30 mL) was refluxed in a Dean-Stark apparatus with dibutyl tin dichloride (0.03 g) for 12 days. The solvent was distilled off and the residue soon solidified. A column chromatography (eluant, cyclohexane-ethyl acetate 1:1) gave **3a** as white crystals from cyclohexane/pentane (0.47 g - 65% yield), m.p. 126-7 °C. ^{1}H-Nmr, δ: 7.2-7.35 (5H, aromatic protons), 5.63 (1H, d, J = 9.8 Hz, H_5), 4.48 (1H, dq, J = 7 and 9.8 Hz, H_4), 1.71 (3H, s, Me), 0.78 (3H, d, Me_4). Elem. anal.: calc. for $C_{23}H_{26}N_2O_2$: C, 76.2; H, 7.2; N, 7.7. Found: C, 76.1; H, 7.1; N, 7.7%. $[\alpha]_D$ = + 359.9° (c = 0.6, chloroform).

*2,2-Bis{2-[4(R)-methyl-5(R)-phenyl-1,3-oxazolinyl]}propane (**4a**).* Bis-amide **2a** (0.8 g - 2 mmol) was suspended in dichloromethane (20 mL) and triethylamine (1.0 g - 10 mmol) under nitrogen stream. Under stirring and keeping the temperature below 0 °C, methanesulfonyl chloride (0.36 mL - 4.6 mmol) was added with a calibrated syringe, then stirring was continued at room temperature for additional 4 hours. The reaction mixture was decomposed with water, extracted with dichloromethane (3 x 50 mL), and the combined organic layers dried and evaporated. The residue was dissolved in ethanol (20 mL) and dropwise NaOH (0.38 g) in water (10 mL) was added. After 3 hours reflux, the ethanol was distilled off and the residue was extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with HCl 3%, then with 5% aqueous $NaHCO_3$ and water, dried and the solvent distilled off. The oilly residue was column chromatographed (eluant, cyclohexane-ethyl acetate 65:35) and the first fraction eluted was crystallized from pentane. **4a** was obtained as white crystals (0.52 g - 72% yield), m.p. 53-4 °C. ^{1}H-Nmr, δ: 7.3 (5H, aromatic protons), 4.93 (1H, d, J = 8.0 Hz, H_5), 4.03 (1H, dq, J = 6.8 and 8.0 Hz, H_4), 1.65 (3H, s, Me), 1.38 (3H, d, Me_4). Elem. anal.: calc. for $C_{23}H_{26}N_2O_2$: C, 76.2; H, 7.2; N, 7.7. Found: C, 76.2; H, 7.3; N, 7.7%. $[\alpha]_D$ = -24.9° (c = 0.6, chloroform).

When the reaction was performed with aged methanesulfonyl chloride, a second fraction was eluted and **5a** crystallized from ligroin-cyclohexane as white crystals, m.p. 135-6 °C. I.r.: $\nu_{OH,NH}$ = 3420 and 3190 cm^{-1}; ν_{CO} = 1675 cm^{-1}. ^{1}H-Nmr, δ: 7.2-7.45 (10H, aromatic protons), 7.35 (overlapped by aromatics and determined by decoupling experiments, 1H, NH), 4.92 (1H, d, J = 7.3 Hz, H_5), 4.57 (1H, d, J = 6.5 Hz, $H_{2'}$), 4.13 (1H, ddq, J = 6.5, 6.8, and 8 Hz, $H_{1'}$), 4.04 (1H, dq, J = 6.8 and 7.3 Hz, $H_{2'}$), 1.51 and 1.50 (6H, s + s, Me), 1.36 (3H, d, J = 6.8 Hz, Me_4), 1.09 (3H, d, J = 6.8 Hz, $Me_{1'}$). Elem. anal.: calc. for $C_{23}H_{28}N_2O_3$: C, 72.6; H, 7.4; N, 7.4. Found: C, 72.7; H, 7.4; N, 7.5%. $[\alpha]_D$ = -9.3° (c = 0.63, chloroform). This product, treated as above with 1 mol of methansulfonyl chloride, gave **4a** with 25% yield.

*2,2-Bis{2-[4(S)-methyl-5(S)-phenyl-1,3-oxazolinyl]}propane (enantiomer of **4a**).* This was obtained from the Aldrich (1*R*,2*S*)-norephedrine 99% purity that was transformed into the enantiomer of **2a**, $[\alpha]_D$ =

-61.5° (c = 0.62, chloroform). Following the method above described, the amide was converted into the enantiomer of **4a**. $[\alpha]_D$ = +24.7° (c = 0.64, chloroform).

2,2-Bis{2-[4(R),5(S)-diphenyl-1,3-oxazolinyl]}propane (3b). This was obtained from **2b** following the Masamune method.[7b] **2b** (1.04 g - 2 mmol), dissolved in anhhydrous xylene (40 mL) was refluxed in a Dean-Stark apparatus with dibutyl tin dichloride (0.04 g) for 43 hours. The solvent was distilled off and the residue was column chromatographed (eluant, cyclohexane-ethyl acetate 8:2). **3b** was obtained as white crystals from cyclohexane (0.70 g - 75% yield), m.p. 152-3 °C (lit.[7b] 155-6 °C). ^{1}H-Nmr, δ: 7.02 and 6.96 (10H, aromatic protons), 5.98 (1H, d, J = 10 Hz, H_5), 5.60 (1H, d, H_4), 1.93 (3H, s, Me), nearly identical to the literature data.[7b] $[\alpha]_D$ = + 303° (c = 0.8, dichloromethane), lit.[7b] $[\alpha]_D^{25}$ = + 367° (c = 1.05, dichloromethane).

2,2-Bis{2-[4(R),5(R)-diphenyl-1,3-oxazolinyl]}propane (4b). Following the method described for **4a**, to **2b** (1.04 g - 2 mmol) in dichloromethane (18 mL) and triethylamine (0.91 g - 9 mmol), methanesulfonyl chloride (0.35 mL - 4.4 mmol) was added with a calibrated syringe, then stirring was continued at room temperature for additional 4 hours. To the oily residue (1.26 g) obtained after work-up of the reaction mixture dissolved in ethanol (40 mL) a solution of NaOH (0.40 g) in water (10 mL) was added. After 3 hours reflux the residue was column chromatographed (eluant, cyclohexane-ethyl acetate 93:7), and **4b** was obtained (0.83 g - 86% yield) as colourless crystals, m.p. 103 °C from cyclohexane. ^{1}H-Nmr, δ: 7.2-7.35 (10H, aromatic protons), 5.33 (1H, d, J = 7.8 Hz, H_5), 5.11 (1H, d, H_4), 1.89 (3H, s, Me). Elem. anal.: calc. for $C_{33}H_{30}N_2O_2$: C, 81.5; H, 6.2; N, 5.8. Found: C, 81.3; H, 6.3; N, 5.7%. $[\alpha]_D$ = +124.3° (c = 0.35, dichloromethane).

ACKNOWLEDGEMENTS

We are grateful to the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) and to the Consiglio Nazionale delle Ricerche (CNR) for the financial support of this research.

REFERENCES AND NOTES.

1) a) Lowenthal, R.E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005; b) Evans, D.A.; Woerpel, K.A.; Hinman, M.M.; Faul, M.M. *J. Am. Chem. Soc.* **1991**, *113*, 726; c) Piquè, C.; Fähndrich, B.; Pfaltz, A. *Synlett* **1995**, 491, and references therein.

2) Von Matt, P.; Lloyd-Jones, G.C.; Minidis, A.B.E.; Pfaltz, A.; Macko, L.; Meuburger, M.; Zehnder, M.; Rüegger, H.; Pregosin, P.S. *Helv. Chim. Acta* **1995**, *78*, 265, and references therein.

3) a) Helmchen, G.; Krotz, A.; Gauz, K.T.; Hansen, D. *Sinlett* **1991**, 257; b) Corey, E.J.; Zhe, W. *Tetrahedron Lett.* **1993**, *34*, 4001.

4) a) Evans, D.A.; Faul, M.M.; Bihodean, M.T. *J. Am. Chem. Soc.* **1994**, *116*, 2742; b) Hansen, K.B.; Finney, N.S.; Jacobsen, E.N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 676, and references therein.

5) a) Corey, E.J.; Imai, N.; Zhang, N.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728; b) Corey, E.J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807; c) Evans, D.A.; Miller, S.J.; Lectka, T.J. *J. Am. Chem. Soc.*, **1993**,

115, 6460; d) Evans, D.A.; Murry, J.A.; von Matt, P.; Norcross, R.D.; Miller, S.J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798; e) Davies, I.W.; Senanayake, C.H.; Larsen, R.D.; Verhoeven, T.R.; Reider, P.J. *Tetrahedron Lett.* **1996**, *37*, 1725; f) Desimoni, G.; Faita, G.; Righetti, P.P. *Tetrahedron Lett.* **1996**, *37*, 3027.

6) Johannsen, M.; Jørgensen, K.A. *J. Org. Chem.* **1995**, *60*, 5757.
7) a) Lowenthal, R.E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373; b) Masamune, S.; Lowenthal, R.E. *U.S. Pat.* 5298623 (1994); *C.A.* **1994**, *121*, 205742.
8) Davies, I.W.; Senanayake, C.H.; Larsen, R.D.; Verhoeven, T.R.; Reider, P.J. *Tetrahedron Lett.* **1996**, *37*, 813.
9) Hall, J.; Lehn, J.M.; De Cian, A.; Fischer, J. *Helv. Chim. Acta* **1991**, *74*, 1.
10) The overall reaction was also performed with (1*R*,2*S*)-norephedrine and, following the same protocol, the enantiomer of **4a**, 2,2-bis{2-[4(R)-methyl-5(R)-phenyl-1,3-oxazolinyl]}propane, was obtained whose rotatory power is obviously the opposite of that reported for **4a**.
11) Smedley, I. *J. Chem. Soc.* **1910**, *97*, 1492.
12) Denmark, S.E.; Nakajima, N.; Nicaise, O.J.-C.; Frencher, A.-M.; Edwards, J.P. *J. Org. Chem.* **1995**, *60*, 4884.

(*Received in UK* 3 *June* 1996; *revised* 10 *September* 1996; *accepted* 12 *September* 1996)