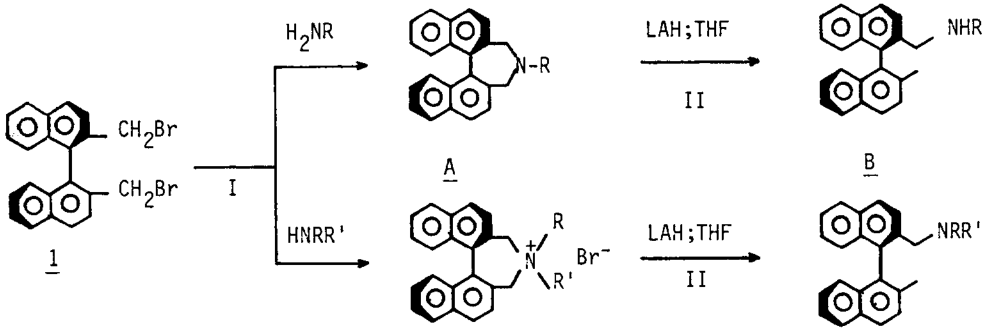
Tetrahedron Letters,Vol.26,No.4,pp 421-424,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain ©1985 Pergamon Press Ltd.

REDUCTIVE CLEAVAGE OF AXIALLY DISYMMETRIC TERTIARY AMINES AND QUATERNARY AMMONIUM SALTS BY LITHIUM ALUMINIUM HYDRIDE. SYNTHESIS OF NEW 1,1'-BINAPHTHYL SUBSTITUTED AMINES

Frédéric COTTINEAU, Nicole MAIGROT and Jean-Paul MAZALEYRAT*(1)
GR 12, C.N.R.S., 2, rue H.-Dunant, 94320 Thiais (France)

Abstract : Axially disymmetric tertiary amines or quaternary ammonium salts A are synthesized by double alkylation of primary or secondary amines with racemic or optically pure 2,2'-bis(bromomethyl)-1,1'-binaphthyl. Their reductive cleavage by lithium aluminium hydride in refluxing THF leads to chiral secondary or tertiary amines B, substituted by a binaphthyl unit, with high yields and absence of racemization.

The rigidity and the axial chirality associated with the 1,1'-binaphthyl unit are potentially useful in asymmetric synthesis, and for the past few years, high asymmetric inductions have been obtained in a variety of reactions, by using as chiral auxiliaries, atropisomeric compounds containing a binaphthyl moiety (2, 3). Efforts have also been made in order to develop new synthesies of binaphthyl derivatives(3a, 4) but the number of available structures is still restricted. Actually, derivatives of (bis)-2-naphthol have been mostly used up to now (2a-h) but 2,2'-bis(bromomethyl)-1,1'-binaphthyl 1 has also been considered as an interesting key intermediate(2h, 3). This compound is available in its racemic(5, 6) as well as optically pure form(6), and it has been shown to react with primary or secondary amines to give bis-alkylated tertiary amines(3b) or quaternary ammonium salts(3c, 6) of type A (reaction I), which have been successfully used as external chiral auxiliaries in asymmetric synthesis(3b,c).



In the present paper, we report further examples of Reaction I, as well as the reductive cleavage of the seven-membered ring of compounds A by lithium aluminium hydride in refluxing THF, leading to secondary or tertiary amines of type B, substituted by a chiral binaphthyl unit (reaction II). No racemization of the binaphthyl skeleton occurs under these experimental

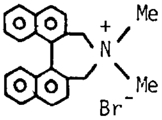
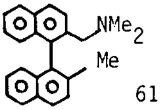
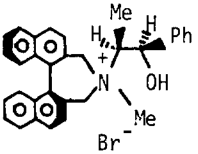
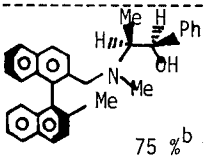
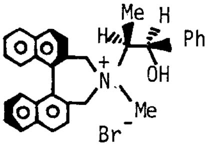
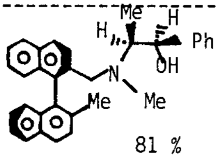
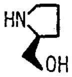
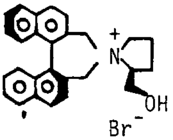
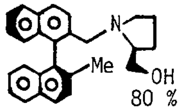
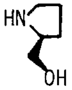
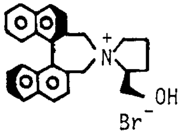
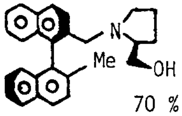
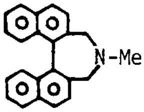
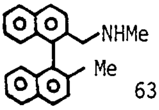
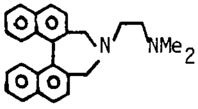
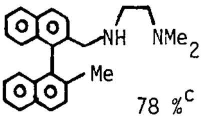
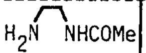
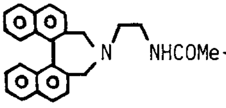
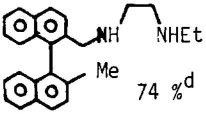
Starting Materials (C.Y.[a] Reaction I)	Compounds A(ref. 8)				Compounds B(ref. 8)	C.Y.[a]
(R,S)1 ; $HNMe_2$ (75 %)	2A (R,S)		LAH ; THF → ⇅23 h	2B (R,S)		61 %
(S)1 ; (1)-ephedrine(1R;2S) (86 %)(ref.3c)	3A (S;1R;2S)		-"- → ⇅ 23 h	3B (S;1R;2S)		75 %[b]
(R)1 ; (1)-ephedrine(1R;2S) (88 %)(ref.3c)	4A (R;1R;2S)		-"- → ⇅ 23 h	4B (R;1R;2S)		81 %
(S)1 ; (S)  (46 %)	5A (S;2S)		-"- → ⇅ 20 h	5B (S;2S)		80 %
(R)1 ; (S)  (69 %)	6A (R;2S)		-"- → ⇅ 20 h	6B (R;2S)		70 %
(R,S)1 ; H_2NMe (72 %)	7A (R,S)		-"- → ⇅ 23 h	7B (R,S)		63 %
(R,S)1 ;  (88 %)(ref.3b)	8A (R,S)		-"- → ⇅ 65 h	8B (R,S)		78 %[c]
(R,S)1 ;  (86 %)	9A (R,S)		-"- → ⇅ 24 h	9B (R,S)		74 %[d]

Table. a.Chemical yield of isolated product. B. 68% yield after 72 h·reflux. c. 50% yield in a duplicate experiment with $NiCl_2$ added. d. No reductive cleavage occurs at room temperature where the only reduction of the amide group leads to the corresponding diamine 10A (71 %).

conditions ; thus reaction II provides an easy access to a new serie of 2,2'-disymmetrically substituted 1,1'-binaphthyls.

As previously described(3b,c , 6), treatment of either racemic or optically pure dibromide 1 by 2 equivalents(7a) of primary or secondary amines in refluxing benzene or benzene-acetonitrile(7b) led to compounds A with high yields (see Table).

Compounds A (1 to 2 mmole scale) were added to a solution of $LiAlH_4$ (10 eq.mol./mol.) in tetrahydrofuran. The mixture was refluxed for ca.24 h (see Table). Hydrolysis with H_2O/THF followed by filtration and evaporation of THF led to a crude product which was dissolved in ether, and extracted with 10 N HCl. The acidic solution was diluted in water, neutralized with an excess of aq. NaOH, and extracted with ether, leading to chemically pure amines B(8) listed in the table.

The structures of compounds B were readily determined from their ^{1}HNMR spectra : the methyl Ar-CH_3 and methylene Ar-CH_2-NRR' groups always appear as singlets at ca.2.0 ppm and 3.4 ppm respectively, instead of a AB quartet at ca.3.2 and 3.7 ppm (J=12 Hz) which is always observed for the methylene $(Ar\text{-}CH_2)_2NR$ group of the corresponding amines A.

Prolonged heating resulted in lower yields, because of a further reductive cleavage leading to the formation of 2,2'-dimethyl-1,1'-binaphthyl. Although this compound was detected in the neutral part of the extraction procedure in all the experiments, its formation was more of a problem in the case of the quaternary ammonium salts 2A-6A, where the primary product is a tertiary amine.

The absence of racemization of the binaphthyl moiety under these experimental conditions is certain, based on the formation of a single diastereoisomer of the amines 3B,4B,5B and 6B. For example, the cleavage of 3A(S;1R;2S) gives only 3B(S;1R;2S), with no trace of 4B (R;1R;2S) which would result from racemization of the binaphthyl unit. Furthermore 2,2'-dimethyl-1,1'-binaphthyl recovered from this reaction is optically pure(9). The observed retention of optical purity of the binaphthyl skeleton is not surprising, considering the very high rotation barriers associated with 2,2'-alkylated-1,1'-binaphthyls(6 , 10).

Reductive cleavage of quaternary ammonium salts by $LiAlH_4$ is well documented(11), but cleavage of allyl tertiary amines generally occurs only in presence of catalytic $NiCl_2$ and cleavage of benzyl tertiary amines is even more difficult(12). In the present case, chemical yields are relatively high, and the reaction is clean enough to represent a synthetic method. This method presents some advantages over the catalytic debenzylation of compounds A with H_2/Pd-C or $Pd(OH)_2$-C in which the bis-debenzylation is more difficult to avoid and in which competitive hydrogenation of the naphthalene rings occurs(13).

In conclusion, reactions(I) and (II) provide straightforward access to 1,1'-binaphthyl substituted secondary or tertiary amines A and B from the dibromide 1. Studies to utilize these substances as chiral auxiliaries in asymmetric synthesis are in progress(14).

References and notes

(1) We wish to dedicate this paper to Zoltan Welvart, who died on April 21st, 1984.

(2) (a) D.S. Lingenfelter, R.C. Helgeson and D.J. Cram, J.Org.Chem.,46,393(1981). (b) D.J.Cram and G.D.Y.Sogah, J.Chem.Soc.Chem.Comm.,625(1981). (c)J.P.Vigneron and I.Jacquet, Tetrahedron, 32,939(1976). (d) R.Noyori, I.Tomino and Y.Tanimoto, J.Amer.Chem.Soc.,101,3129 (1979) (e) A.Miyashita, A. Yasuda, H.Takaya, K.Toriumi, T.Ito, T.Souchi and R.Noyori, J.Amer.Chem.

Soc.,102, 7932 (1980). (f) A.G.Olivero, B.Weidmann and D. Seebach, Helv.Chim.Acta, 64, 2485(1981). (g) M.Amano, M.Watanabe, N.Baba, J.Oda and Y.Inouye, Bull.Chem.Soc.Jpn.,56, 3672(1983). (h) S.Sakane, J.Fujiwara, K.Maruoka and H.Yamamoto, J.Amer.Chem.Soc., 105, 6154 (1983).

(3) (a) K. Tamao, H.Matsumoto, N.Miyake, T.Hayashi and M.Kumada,Tetrahedron Lett., 1389(1977) (b) J.P.Mazaleyrat and D.J.Cram, J.Amer.Chem.Soc., 103, 4585 (1981). (c) J.P. Mazaleyrat, Tetrahedron Lett., 24, 1243 (1983).

(4) (a) B.Feringa and H.Wynberg, Bioorg.Chem., 7,397(1978). (b)S.Miyano, M.Tobita and H.Hashimoto, Bull.Chem.Soc.Jpn., 54,3522(1981). (c) J.Brussee and A.C.A.Jansen, Tetrahedron Lett.,24,3261(1983). (d) J.M.Wilson and D.J.Cram, J. Amer. Chem. Soc., 104, 881(1982). (e) A.I.Meyers and K.A.Lutomski, J.Amer.Chem.Soc., 104,879(1982). (f) A.I.Meyers and D.G. Wettlaufer, J.Amer.Chem.Soc.,106, 1135 (1984).

(5) H.J.Bestmann and W. Both, Chem. Ber., 107, 2926 (1974).

(6) D. M. Hall and E.E. Turner, J. Chem. Soc., 1242 (1955).

(7) (a) Excess of amine is used in order to neutralize the ammonium hydrobromide obtained from the initial substitution process, but the reaction also works with one equivalent of amine plus triethylamine. Bis-aminated binaphthyls of type $(R'RN\text{-}CH_2\text{-}Ar)_2$ are never formed even when a very large excess of amine is present ; apparently, the intramolecular process of the second substitution, leading to a seven membered cyclic amine or ammonium, is much faster than the potentially competitive intermolecular process, probably for conformational reasons. (b) the reaction is accelerated by addition of acetonitrile.

(8) 2A: m.p.315-320°C(decomp.);^{1}HNMR:5.45 and 3.75,dd(J=12Hz),$Ar\underline{CH}_2$;3.67,s,$\overset{+}{N}(\underline{CH}_3)_2$.3A-4A:ref 3c.5A:m.p.255-260°C(EtOH): $[\alpha]^{22}_{546}$=+481°(c1.3;EtOH);MS:380(M^+-80).6A:m.p.274-275°C(EtOH-acetone); $[\alpha]^{22}_{546}$=-532°(c1;EtOH). 7A:MS:309(M^+);^{1}HNMR:3.57 and 3.17,dd(J=12Hz),$Ar\underline{CH}_2$;2.37, s,$N\underline{CH}_3$;m.p.(picrate):202-204°C(EtOH). 8A$^{(3b)}$:^{1}HNMR:3.73 and 3.20,dd(J=12Hz),$Ar\underline{CH}_2$;2.27, s,$N\underline{CH}3$. 9A:m.p.187-189°C(Et_2O-benzene);MS:380(M^+);^{1}HNMR:3.70 and 3.20,dd(J=12Hz),$Ar\underline{CH}_2$; 2.02,s,$NCO\underline{CH}_3$. 10A:MS:366(M^+);^{1}HNMR:3.68 and 3.18,dd(J=12Hz),$Ar\underline{CH}_2$. 2B:MS:325(M^+);^{1}HNMR :3.10,s,$Ar\underline{CH}_2$;2 03,s,$N(CH_3)_2$. 3B:MS:463(M^++18(NH_4^+));$[\alpha]^{22}_{546}$=-47.4°(c0.9;EtOH);^{1}HNMR:3.35, s,$Ar\underline{CH}_2$;2.04,s,$Ar\underline{CH}_3$;2.05,s,$N\underline{CH}_3$. 4B: $[\alpha]^{22}_{546}$=+18.7°(c1;EtOH);^{1}HNMR:3.34,s,$Ar\underline{CH}_2$;2.01,s, $Ar\underline{CH}3$;2.07,s,$N\underline{CH}_3$.5B:MS:381(M^+); $[\alpha]^{22}_{546}$=+107°(c1.2;EtOH);^{1}HNMR:2.02,s,$Ar\underline{CH}_3$. 6B: $[\alpha]^{22}_{546}$= -204°(c1.2;EtOH);^{1}HNMR:2.03,s,$ArCH_3$. 7B:MS:311(M^+);^{1}HNMR:3.50,s,$Ar\underline{CH}_2$;2.02,s,$Ar\underline{CH}_3$;2.17, s,$N\underline{CH}_3$. 8B: MS:368(M^+);^{1}HNMR:3.48,s,$Ar\underline{CH}_2$;2.05,s,$Ar\underline{CH}_3$;2.02,s,$N(\underline{CH}_3)_2$.9B:MS:368(M^+); ^{1}HNMR:3.50,s,$Ar\underline{CH}_2$;2.05,s,$Ar\underline{CH}_3$.

(9) Further investigation of this reaction is in progress; the overall process could constitute an interesting alternative way for obtaining optically pure 2,2'-dimethyl-1,1'-binaphthyl and its derivatives.

(10) W. Dixon, M. M. Harris and R.Z. Mazengo, J. Chem. Soc. (B), 775 (1971).

(11) N.G. Gaylord,"Reduction with Complex Metal Hydrides", Interscience Publishers, Inc., New-York, 1956, pp. 781-793.

(12) V.L. Tweedie and J.C. Allabashi, J. Org. Chem., 26, 3676 (1961).

(13) N. Maigrot and J.P. Mazaleyrat, unpublished results.

(14) The quaternary ammonium salts A and those resulting from quaternarization of amines A and B represent a class of new potentially interesting chiral phase transfer catalysts$^{(3c)}$.

(Received in France 23 June 1984)