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$TiCl_4$ Induced Opening of Chiral Acetals: a route to β-adrenergic blocking agents

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Abstract : Aryloxy and alkyloxypropanolamines 7a-c are obtained in 45 to 70% yields and with 80% of asymmetric induction, using $TiCl_4$ induced nucleophilic addition of cyanotrimethylsilane onto chiral acetals derived from racemic 2,4-pentanediol. Therefore, optically pure 2,4-pentanediol will provide, after a purification, optically pure 7a-c.

Optically pure β-adrenergic blocking agents of the type aryloxy and alkyloxy-propanolamines are usually synthesized in poor yields (4 to 15%) from D-mannitol[1-5] or vitamin-C[6]. The first efficient asymmetric synthesis of 2S-propanolol (50% yield announced) has been recently proposed by Sharpless and coll.[7] which prompted us to report some results obtained in this field[8].

We found that optically pure aryloxy and alkyloxypropanolamine 7a-c can be obtained, after a purification, in satisfactory yields (40 to 65%) using $TiCl_4$ induced opening of optically pure chiral acetals.

Chiral acetals have been first used as inducers of chirality by Johnson and coll.[9-11], and of particular interest for us was the use, as a nucleophile, of cyanotrimethylsilane because the products could be converted into chiral aminoalcohols of high optical purity[12,13].

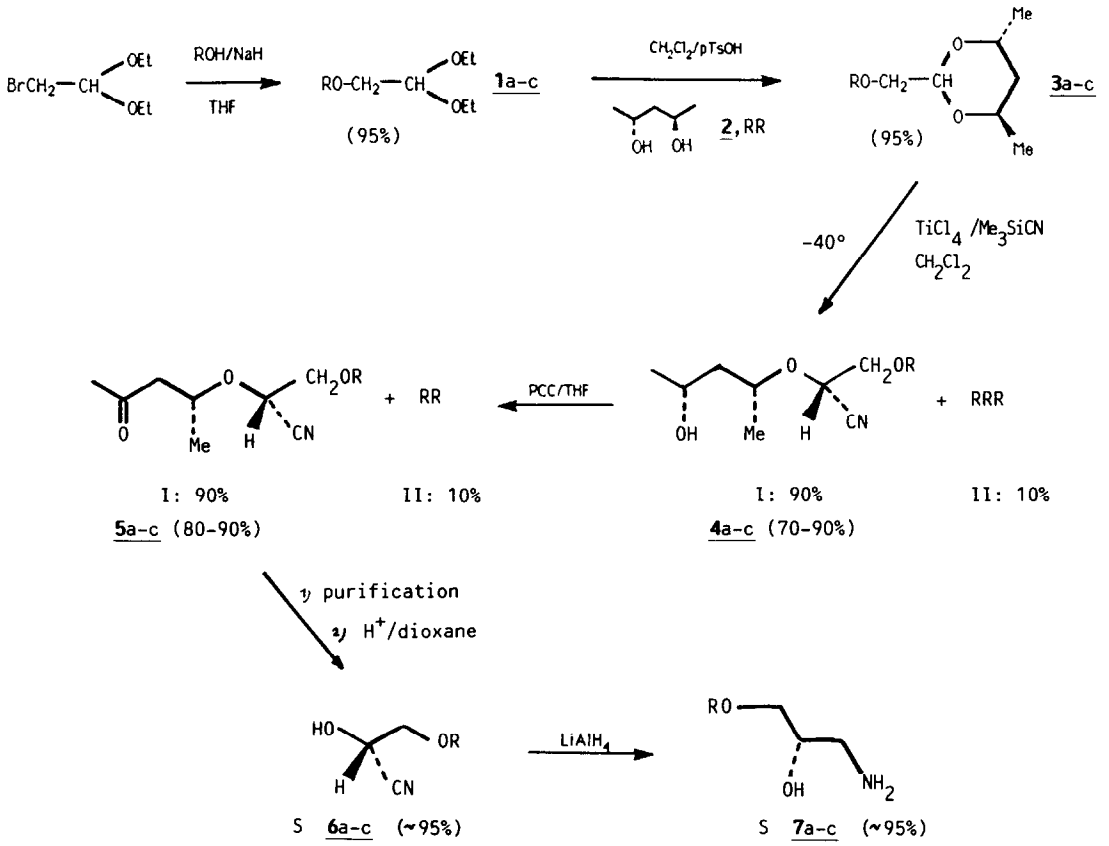
Therefore, the synthetic scheme (scheme 1) is relatively straightforward and the challenge was to perform the coupling-step-3 in the presence of an ether function.

The chiral ether-acetals 3a-c[14] are obtained in about 95% yield by an acid-catalyzed exchange reaction and have been purified by column chromatography before being used for the following step. $TiCl_4$ induced nucleophilic additions of cyanotrimethylsilane are then carefully performed (temperature, rate of addition and waiting time must be optimized) leading to compounds 4a-c[15] in 70 to 90% yield. After PCC oxidation, compounds 5a-c[16] are obtained in 80 to 90% yield.

Diastereomer-ratios are determined by H-1 NMR (200MHz) on compounds 5a-c, before and after purification, but because of serious overlaps, $Eu(FOD)_3$ must be used in the case of

compounds 4 (the results obtained from 4 and from 5 are consistent[15,16]). Finally, acidic β-elimination followed by reduction give 7a-c in 90% yield.

Scheme 1 (a :R= $(CH_3)_2CH$; b :R= $(CH_3)_2CH-CH_2$; c :R= C_6H_5)



Racemic 2,4-pentanediol has been used during this work and racemic aminoalcohols 7 are obtained[17] however, the main diastereomers of compounds 5a-c being obtained pure after a chromatographic purification, one can conclude that optically pure 2,4-pentanediol will afford optically pure alcohols 7. According to the model of Johnson and coll.[12] one can also postulate that the RR diol will give the S aminoalcohols as the major compounds (90%), which is the desired absolute configuration for those β-blockers.

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REFERENCES

1) K. Yamamoto, T. Uno, T. Ishihara and K. Nakagawa ; Yakugaku Zashi, 96 289 (1976).

2) L.M. Weinstock, D.M. Mulvey and R. Tull ; J. Org. Chem., 41, 3121 (1976).

3) J.J. Baldwin, D.E. McLure, D.M. Gross and M. Williams ; J. Med. Chem., 25, 931 (1982).

4) B.W. Kiersted, A. Fararoe, F. Mennoma, J. Mullin, R.W. Guthrie, H. Crowley, B. Simko and L.C. Blaben ; J. Med. Chem., 26, 1561 (1983).

5) M. Bouzoubaa, G. Leclerc, S. Rakhit and G. Andermann, J. Med. Chem., 28, 27 (1984).

6) M.E. Jung and T.J. Shaw ; J. Am. Chem. Soc., 102, 6304 (1980).

7) J.M. Klunder, S.Y. Ko and K.B. Sharpless ; J. Org. Chem., 51, 3710 (1986).

8) This research was initiated in 1985 by Dr. J. Suffert during his post-doctoral work and continued by M. Gordon on a grant from Alcon R & D France.

9) W.S. Johnson, C.A. Harbert and R.D. Stipanovic ; J. Am. Chem. Soc., 90, 5279 (1968).

10) W.S. Johnson, R. Elliott and J.D. Elliott, J. Am. Chem. Soc., 105, 2904 (1983).

11) J.D. Elliott, V.M.F. Choi and W.S. Johnson ; J. Org. Chem., 48, 2294 (1983).

12) W.M.F. Choi, J.D. Elliott and W.S. Johnson ; Tetrahedron Letters, 25, 591 (1984).

13) A. Solladié-Cavallo, A.C. Dreyfus, F. Sanch and A. Klein, Chem. Letters, 1583 (1987)

14) H-1 NMR 200MHz (Bruker WP-200 SY) $CDCl_3$/TMS δ ppm.

3a : 1.17 ($2CH_3$, d, iPr, J=6Hz), 1.22 (CH_3 ring, d, J=6Hz), 1.31 (CH_2 ring, $H_{eq.}$,m), 1.38 (CH_3 ring, d, J=6.5Hz), 1.85 (CH_2 ring, H_{ax}, d.d.d., J=12Hz, 6.5Hz, ^2J=-13Hz), 3.44 (CH_2, A_2 part of A_2X, d, J=4.5Hz), 3.64 (CH, iPr, sept., J=6Hz), 3.99 (CH ring, H_{ax}, q.d.d, J=6Hz, 12Hz, 2.5Hz), 4.32 (CH ring, $H_{eq.}$, quint. J=6.5Hz, 6.5Hz, 0Hz), 5.01 (CH, X part of A_2X, t, J=4.5Hz).

3b : 0.89 ($2CH_3$, iBu, d, J=6.5Hz), 1.21 (CH_3 ring, d, J=6Hz), 1.32 (CH_2 ring, $H_{eq.}$,m), 1.38 (CH_3 ring, d, J=6.5Hz), 1.86 (CH_2 ring, H_{ax}, d.d.d., J=12Hz, 6Hz, ^2J=-13.5Hz and CH, iBu, m), 3.25 (CH_2, iBu, d, J=6.5Hz), 3.44 (CH_2, AB part of ABX, ^2J=-12Hz), 4.00 (CH ring, H_{ax}, q.d.d., J=6Hz, 12Hz, 2.5Hz), 4.32 (CH ring, $H_{eq.}$, quint., J=6.5Hz, 6.5Hz, 0Hz), 5.03 (CH, X part of ABX, J=4.5Hz).

3c : 1.23 (CH_3 ring, d, J=6Hz), 1.35 (CH_2 ring, $H_{eq.}$ m.), 1.40 (CH_3 ring, d, J=6.5Hz), 1.89 (CH_2 ring, H_{ax}, d.d.d., J=6.5Hz, 12Hz, ^2J=-13.5Hz), 4 (CH_2, AB part of ABX and CH ring $H_{ax.}$ m), 4.36 (CH ring, $H_{eq.}$, quint, J=6.5Hz, 6.5Hz, 0Hz), 5.23 (CH, X part of ABX, t, J=4.5Hz), 6.94 (aromat. 3H, m), 7.25 (aromat. 2H, m).

15) H-1 NMR, 200MHz (Bruker WP-200 SY) ($CDCl_3$/TMS δ ppm.

4a : 1.18 (CH_3, d, J=6.5Hz), 1.20 ($2CH_3$, iPr, d, J=6Hz), 1.33 (CH_3, d, J=6Hz), 1.61 (CH_2, AB part of ABXY where J_{XY}=0, m, this chain corresponds to the opened acetal), 2.77 (OH), 3.70 (CH_2, AB part of ABX and CH iPr, m), 3.95 and 4.10 (multiplet 2 CH on the chain corresponding to the opened acetal), 4.35 (CH, X part of ABX).

4b : 0.93 ($2CH_3$, iBu, weakly non-equivalent, two close d., J=6.5Hz), 1.20 (CH_3, d, J=6Hz), 1.35 (CH_3, d, J=6Hz), 1.60 (CH_2, AB part of ABXY where J_{XY}=0, m, this chain corresponds to the opened acetal), 1.90 (CH, iBu, nonuplet, J=6.5Hz), 2.5 (OH), 3.30 (CH_2, AB part of $ABXK_6$, isobutyl chain, J_{AB}=-11Hz, J ≃ 6.5Hz), 3.70

(CH_2, AB part of ABX, J_{AB}=-10Hz, J ≃ 4.5Hz, 7.5Hz), 4.0 and 4.1 (multiplets, 2CH, X and Y part of ABXY, opened acetal), 4.3 (CH, X part of ABX, J ≃ 4.5Hz, 7.5Hz).

4c : 1.19 (CH_3, d, J=6Hz), 1.36 (CH_3, d, J=6Hz), 1.62 (CH_2, AB part of ABX_2 where J_{XX} = 0, m, opened acetal), 2.00 (OH), 4.05 (m, 2CH, X part of ABX_2, opened acetal), 4.23 (CH_2, A_2 part of A_2X, J=6Hz), 4.63 (CH, t, X part of A_2X, J=6Hz), 6.92 (2H arom., d), 7.01 (1H arom., ≃t), 7.27 (2H arom., ≃ t).

4c + $Eu(FOD)_3$.

First the triplet at 4.63 split into two triplets, ratio 87/19. Then the methyls doublets split into two doublets each, ratio 90/10 and 91/9.

16) H-1 NMR, 200MHz (Bruker WP-200 SY), $CDCl_3$/TMS δ ppm.

5a : 1.17 ($2CH_3$, iPr, d, J=6Hz), 1.33 (CH_3, d, J=6Hz), 2.16 and 2.19 (CH_3, s, ratio 91/9), 2.65 (CH_2, AB part of $ABX(K_3)$ opened acetal, $\Delta\nu_{AB}$=56Hz, J_{AB}=-17Hz, J ≃ 4Hz, 8Hz), 3.59 (CH_2, A_2 part of A_2X, d, J=6Hz), 3.65 (CH, iPr, sept., J=6Hz), 4.18 (CH, X part of $ABXK_3$, m), 4.40 (CH, X part of A_2X, t, J=6Hz).

The non equivalence of the two isomers is observed on the AB system but can not be used because of overlap.

5b : 0.90 ($2CH_3$,iBu, d, J=6.5Hz), 1.33 (CH_3, d, J=6Hz), 1.86 (CH iBu, nonuplet, J=6.5Hz), 2.15 and 2.19 (CH_3, s, ratio 88/12), 2,63 (CH_2, AB part of $ABX(K_3)$, opened acetal, $\Delta\nu_{AB}$= 62Hz, J_{AB}=-17Hz, J ≃ 4Hz, 8Hz), 3.25 (CH_2, AB part of $ABXK_6$, isobutyl chain, J_{AB}=-11Hz, J 6.5Hz), 3.60 and 3.64 (CH_2, A_2 part of A_2X, d, J=6Hz, ratio 88/12) 4.20 (CH, X part of $ABXK_3$, m), 4.47 and 4.42 (CH, X part of A_2X, t, J=6Hz, ratio 85/15).

5c : 1.36 and 1.25 (CH_3, d, J=6Hz, ratio 88/12), 2.14 and 2.19 (CH_3, s, ratio 90/10), 2.65 (CH_2, AB part of $ABX(K_3)$, $\Delta\nu_{AB}$=59Hz, J_{AB}=-18Hz, J ≃ 3.5Hz, 8Hz), 4.15 (CH_2, A_2 part of A_2X, d, J=6Hz), 4.25 (CH, X part of $ABXK_3$, m), 4.69 (CH, X part of A_2X, t, J=6hz),, 6.92 (2H arom., ≃d), 7.0 (1H arom., ≃t), 7.30 (2H, arom., ≃ t).

17) Because of the simplicity of the compounds only two examples are given.

H-1 NMR 200MHz (Bruker WP-200 SY), $CDCl_3$/TMS δ ppm.

7a : 1.17 ($2CH_3$, iPr, d, J=6Hz), 2.15 (OH, b), 2.75 (CH_2N, A_1B_1 part an $A_1B_1XA_2B_2$, $\Delta\nu_{AB}$ =22Hz, J_{AB}=-12Hz, J ≃3.5Hz, 7Hz), 3.42 (CH_2O, A_2B_2 part of $A_1B_1XA_2B_2$, $\Delta\nu_{AB}$=18Hz, J_{AB}=-9.5Hz, J≃ 4.5Hz, 7Hz), 3.60 (CH, iPr, sept., J=6Hz), 3.70 (CH, X part of $A_1B_1XA_2B_2$, m).

6a : 1.15 ($2CH_3$, iPr, d, J=6Hz), 3.62 (CH_2, AB part of ABX, $\Delta\nu_{AB}$=16Hz, J_{AB}=-15Hz, J≃ 4Hz, 4Hz), 3.64 (CH, iPr, sept.), 4.52 (CH, X part of ABX, t, J=4Hz).

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