Tetrahedron Letters,Vol.29,No.48,pp 6211-6214,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ENANTIOSELECTIVE CYCLIZATION OF CHIRAL BUTANE-1,4-DIOLS TO CHIRAL TETRAHYDROFURANS: SYNTHESIS OF CHIRAL *TRANS*-2-(3-METHOXY-5-METHYLSULFONYL-4-PROPOXYPHENYL)-5-(3,4,5-TRIMETHOXYPHENYL)TETRAHYDROFURAN (L-659,989), A POTENT PAF-RECEPTOR ANTAGONIST

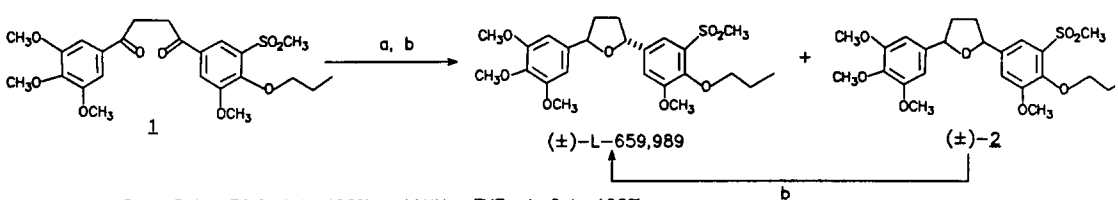
M. M. Ponpipom*, R. L. Bugianesi and J. C. Chabala
Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065 (U.S.A.)

Abstract. Acid catalyzed cyclization of (1*R*,4*RS*)- and (1*S*,4*RS*)-1-(3-methoxy-5-methylsulfonyl-4-propoxyphenyl)-4-(3,4,5-trimethoxyphenyl)butane-1,4-diols to the corresponding chiral *cis*- and *trans*-tetrahydrofurans proceeds with retention of configuration at C-1. Using this stereo- and regioselective reaction, the two optically active enantiomers of L-659,989, a potent PAF-receptor antagonist, were prepared.

Synthesis of chiral lignans of the 2,5-diaryltetrahydrofuran series has been difficult due to the propensity for ionizing racemization during the cyclization reactions of the easily available intermediate butane-1,4-diols, and the tediousness and low capacity of chromatographic separations of THF racemates on chiral supports. We required chiral tetrahydrofurans in order to explore the stereochemical requirements for binding of these compounds to the receptors of platelet activating factor (PAF, 1-*O*-alkyl-2-*O*-acetyl-*sn*-glycero-3-phosphocholine[1]), an important mediator of pathophysiological reactions in several animal disease models and in human disease[2]. In this communication we report that the acid catalyzed cyclization of (1*R*,4*RS*)- and (1*S*,4*RS*)-1-(3-methoxy-5-methylsulfonyl-4-propoxyphenyl)-4-(3,4,5-trimethoxyphenyl)butane-1,4-diols to the corresponding chiral *cis*- and *trans*-tetrahydrofurans proceeds with retention of configuration at C-1. This novel reaction was utilized to prepare both enantiomers of *cis*- and *trans*-2-(3-methoxy-5-methylsulfonyl-4-propoxyphenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran, the latter of which is L-659,989, a highly potent, selective, and competitive PAF-receptor antagonist[3,4].

Diketone **1**[3] can be reduced with $NaBH_4$ in EtOH or $LiAlH_4$ in THF in near quantitative yields (Scheme 1), and the resulting mixture of diols cyclized with 5% trifluoroacetic acid in $CHCl_3$[3,5] to provide a mixture of (±)-*cis*- and (±)-*trans*-2,5-diaryltetrahydrofurans, separable by HPLC (SiO_2; hexane-ethyl acetate, 2:1 [v/v])[6,7]. Isomerization of the *cis*-isomer to a mixture of *cis*- and *trans*- isomers is conveniently effected with 5% trifluoroacetic acid in $CHCl_3$ at room temperature.

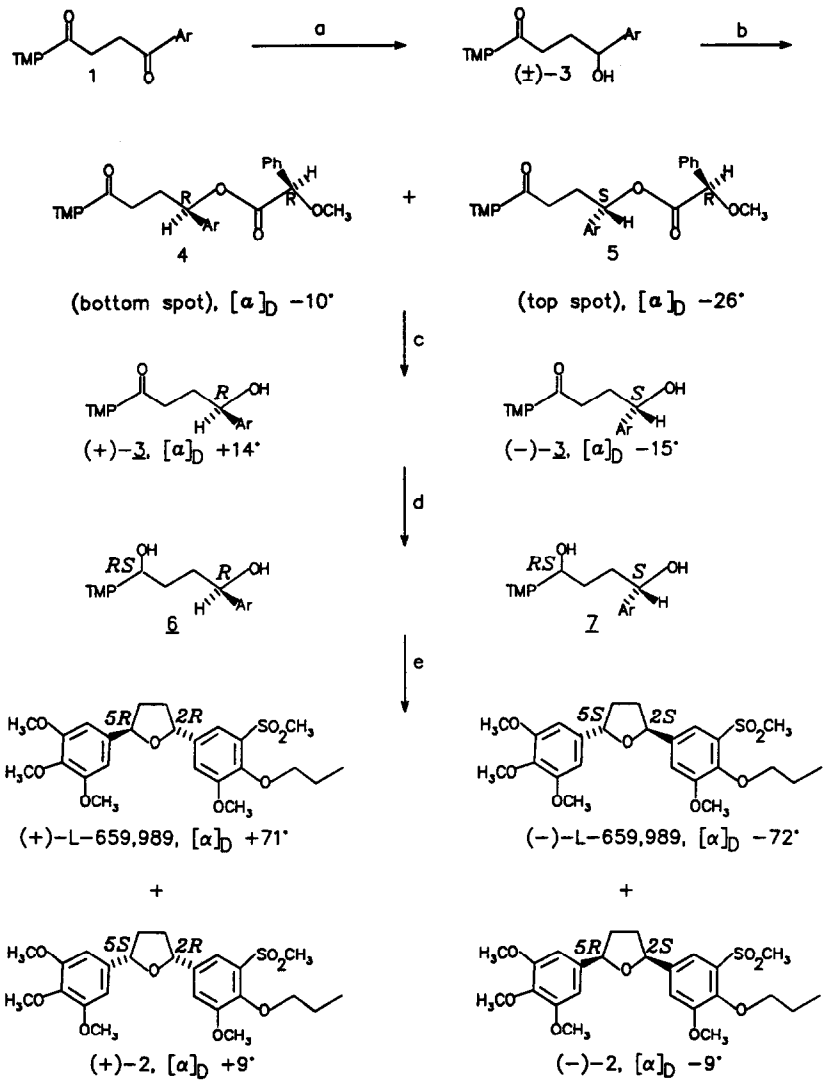
Scheme 1



a = $NaBH_4$, EtOH, 70°C, 1 h, 100% or $LiAlH_4$, THF, rt, 2 h, 100%;
b = 5% CF_3COOH in $CHCl_3$, rt, 35 min, 50% trans + 23% cis.

Although small scale resolution of racemic 2,5-diaryltetrahydrofurans is possible by HPLC on chiral supports[8], large-scale preparations are not feasible. Our solution to this problem was to attempt regioselective reduction of **1** to a single hydroxyketone, resolve *via* chiral mandelate esters[9], and attempt cyclization with retention of configuration at the chiral center. It was anticipated that the electron deficient methylsulfonylphenyl group of **1** would direct hydride

Scheme 2



Ar = 3-methoxy-5-methylsulfonyl-4-propoxyphenyl; TMP = 3,4,5-trimethoxyphenyl; a = $NaBH_4$ (0.4 eq.), EtOH, 45°C, 16 h, 30% or $LiAl(OtBu)_3$, THF, 0°C, 3 h, 70%; b = (−)-R-O-methylmandelic acid. DCC, DMAP, CH_2Cl_2, rt, 2 h, 75% (1:1 mixture); c = KOH, EtOH, 55°C, 15 min, 70%; d = $NaBH_4$, EtOH, 70°C, 0.5 h, 100%; e = 5% CF_3COOH in $CHCl_3$, 0–5°C, 5 h, 70% (trans-cis: 4:1).

reduction to selectively provide (±)-**3** (see Scheme 2). Furthermore, after resolution and further reduction to the diol, the methylsulfonylphenyl group was expected to suppress ionization and racemization at the chiral benzylic center during cyclization. In the event, treatment of **1** with sodium borohydride (0.4 eq, 45°C, 16 h) in ethanol provided (±)-**3**[10] as the only hydroxyketone, although a substantial amount of the diol and the starting **1** were present in the reaction mixture. However, reaction with lithium tri-*t*-butoxyaluminum hydride (1.0 eq., THF, 0°C, 3 h) afforded complete reduction to (±)-**3** with formation of only trace amounts of the alternate hydroxyketone. Esterification of (±)-**3** with (-)-*R*-*O*-methylmandelic acid afforded a mixture of diastereoisomers **4** and **5**, separable by column chromatography. The absolute stereochemistry of **4** and **5** was assigned using the Mosher model[9,11] depicted in the extended Newman projection[12]. The close proximity of the aryl group to the mandelate phenyl moiety of **4** is predicted to induce an upfield shift in the two 3-methoxy-5-methylsulfonyl-4-propoxyphenyl aromatic protons relative to those of **5**, and a downfield shift of the methylene protons of **4** relative to **5**. The anticipated shifts were observed in the NMR spectra[13] of **4** and **5**, permitting the assignment of the (1*R*)-configuration to **4** and the (1*S*)-configuration to **5**. Saponification of mandelates **4** and **5** afforded the corresponding enantiomeric alcohols (+)-**3** (mp 126-127°C, $[\alpha]_D$ +14°) and (-)-**3** (mp 126-127°C, $[\alpha]_D$ -15°) (see Scheme 2). The absolute configuration of (-)-**3** was confirmed by anisotropic scattering during X-ray analysis.

Sodium borohydride reduction of (+)-**3** and (-)-**3** provided diols **6** and **7**, which upon cyclization (5% TFA/$CHCl_3$, 0-5°C, 5 h) provided 4:1 mixtures of chiral *trans*- and *cis*-tetrahydrofurans which exhibited nearly equal but opposite optical rotations (Scheme 2)[14]. Interestingly, equilibration of the 2*R*,5*S*-*cis*-isomer (+)-**2** (10% TFA/$CHCl_3$, 25°C, 1 h) provided a 1:1 ratio of the 2*R*,5*R*-*trans*-isomer, (+)-L-659,989 ($[\alpha]_D$ +72°) and the starting *cis* isomer, (+)-**2** ($[\alpha]_D$ +9°), indicating that no racemization had occurred at C-2. These results also suggest that there is a transfer of stereochemistry upon reduction to the diols, and that cyclization of the diols under these conditions occurs with some stereoselectivity.

The optical purity of (+)-L-659,989 and (-)-L-659,989 was assessed by NMR using tris(3-heptafluorobutyryl-*d*-camphorato)europium (III)[15]. Addition of 0.3 mole of the shift reagent per mole of (±)-L-659,989 induces separation of the sulfone methyl signals with concomitant reduction in signal intensity. Under identical conditions, no such effects were observed with (-)-L-659,989. After addition of 14% (w/w) of (+)-L-659,989 to (-)-L-659,989, separation of the sulfone methyl signals and the reduction of the height intensity is again observed. Assuming that the observed decrease in the sulfone methyl signal intensity of (-)-L-659,989 is linear with increasing amounts of contaminating (+)-L-659,989, the optical purity of (-)-L-659,989 and (+)-L-659,989 are assessed at >95%. The stereochemical specificity of PAF-binding inhibition by (±)-*trans*-L-659,989 was demonstrated by the observation that the *cis*-isomer, (±)-**2**, was about 200-300 times less potent, and also by the fact that (-)-L-659,989 was approximately 20-30 fold more potent than (+)-L-659,989[4].

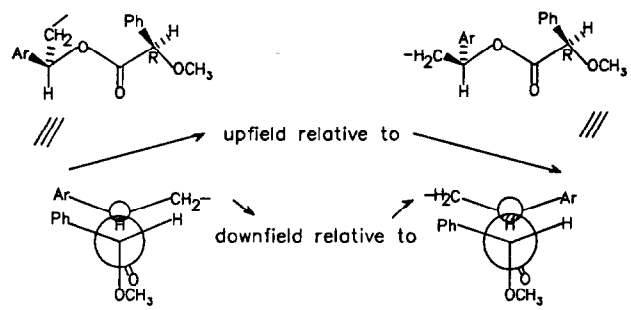
Acknowledgments

The authors thank Ms. V. Riggi for preparing the manuscript, the late Mr. J. Hirshfield for performing x-ray diffraction, Mrs. J. T. Wu and her associates for elementary microanalyses, and Drs. T. Biftu and B. Trost for helpful discussions.

References and Notes

1. C. A. Demopoulos, R. N. Pinckard and D. J. Hanahan, J. Biol. Chem., **254**, 9355 (1979); J. Benveniste, M. Tence, J. Bidault, C. Boullet, P. Varence and J. Polonsky C. R. Seances Acad. Sci., Ser. D, **289**, 1037 (1979).
2. P. Braquet, L. Touqui, T. Y. Shen and B. B. Vargaftig, Pharmacol. Rev., **39**, 97 (1987).
3. K_i of L-659,989 for PAF binding to platelet membranes: 1.1 nM (rabbit) and 9.0 nM (human); diketone **1**: mp 145-146°C, prepared in 5 steps in 22% overall yield from 5-iodovanillin and 3,4,5-trimethoxyacetophenone, M. M. Ponpipom, S.-B. Hwang, T. W. Doebber, J. J. Acton, A. W. Alberts, T. Biftu, D. R. Brooker, R. L. Bugianesi, J. C. Chabala, N. L. Gamble, D. W. Graham, M.-H. Lam and M. S. Wu, Biochem. Biophys. Res. Commun., **150**, 1213 (1988).
4. S.-B. Hwang, M.-H. Lam, A. W. Alberts, R. L. Bugianesi, J. C. Chabala and M. M. Ponpipom, J. Pharmacol & Exp. Ther., **246**, 534 (1988).
5. T. Biftu, N. F. Gamble, T. Doebber, S.-B. Hwang, T. Y. Shen, J. Snyder, J. P. Springer and R. Stevenson, J. Med. Chem., **29**, 1917 (1986).

6. All compounds reported in this communication gave correct microanalyses and exhibited NMR spectral characteristics that were in agreement with their structures. *Cis*-isomer, (±)-**2**: 23% yield, R_f 0.35, mp 150-151°C; NMR ($CDCl_3$): δ 1.05 (t, J = 7.5 Hz, CH_3), 1.89 (m, $CH_2\underline{CH_2}CH_3$), 2.0 and 2.45 (2 m, 4 H, H-3 & H-4), 3.26 (s, SO_2CH_3), 3.86 and 3.87 (2 s, 4 OCH_3), 4.13 (t, J = 7.0 Hz, $\underline{CH_2}CH_2CH_3$), 4.98-5.10 (m, H-2 & H-5), 6.66 (s, 2 H, C_5ArH), 7.25 and 7.61 (2 d, J = 1.5 Hz, 2 H, C_2ArH).
7. *Trans*-isomer, (±)-L-659,989: 50% yield, R_f 0.4, mp 99-100°C; NMR ($CDCl_3$): δ 1.05 (t, J = 7.5 Hz, CH_3), 1.89 (m, $CH_2\underline{CH_2}CH_3$), 1.89 and 2.49 (2 m, 4 H, H-3 & H-4), 3.26 (s, SO_2CH_3), 3.85, 3.89 and 3.93 (3 s, 4 OCH_3), 4.12 (t, $\underline{CH_2}CH_2CH_3$), 5.16-5.28 (m, H-2 & H-5), 6.62 (s, 2 H, C_5ArH), 7.27 and 7.51 (2 d, J = 1.5 Hz, 2 H, C_2ArH).
8. M. M. Ponpipom, B. Z. Yue, R. L. Buglanesi, D. R. Brooker, M. N. Chang and T. Y. Shen, Tetrahedron Lett., **27**, 309 (1986).
9. B. M. Trost, J. L. Belletire, S. Godleski, P. G. McDougal and J. M. Balkovec, J. Org. Chem., **51**, 2370 (1986).
10. Hydroxyketone (±)-**3** had mp 115-117°C and NMR ($CDCl_3$): δ 1.05 (t, J = 7.5 Hz, CH_3), 1.88 (m, $CH_2\underline{CH_2}CH_3$), 2.20 (m, $\underline{CH_2}CHOHAr$), 3.14 (t, $CO\underline{CH_2}$, J = 7.0 Hz), 3.25 (s, SO_2CH_3), 3.92 (s, 4 OCH_3), 4.12 (t, J = 6.5 Hz, $\underline{CH_2}CH_2CH_3$), 4.86 (m, CHOH), 7.23 (s, 2 H, C_4ArH), 7.28 and 7.49 (2 d, J = 1.5 Hz, 2 H, C_1ArH).
11. J. A. Dale and H. S. Mosher, J. Am. Chem. Soc., **95**, 512 (1973).
12. The extended Newman projections of **4** and **5**.



Ar = 3-methoxy-5-methylsulfonyl-4-propoxyphenyl; TMP = 3,4,5-trimethoxyphenyl.

13. Faster moving **5** had NMR ($CDCl_3$): δ 2.17 (m, $\underline{CH_2}CHOM$), 2.65 (t, J = 7.0 Hz, $CO\underline{CH_2}$), 7.07 (d, J = 1.5 Hz, ArH-2), 7.53 (d, ArH-6); slower moving **4** had NMR ($CDCl_3$): d 2.27 (m, $\underline{CH_2}CHOM$), 2.93 (t, J = 7.0 Hz, $CO\underline{CH_2}$), 6.79 (d, J = 1.5 Hz, ArH-2), 7.37 (d, ArH-6).
14. The 2*R*,5*R*-*trans*-isomer, (+)-L-659,989 had mp 73-74°C, $[\alpha]_D$ +71° and its 2*S*,5*S*-enantiomer, (-)-L-659,989 had mp 72-73°C, $[\alpha]_D$ -72°. The 2*R*,5*S*-*cis*-isomer, (+)-**2** had mp 92-93°C, $[\alpha]_D$ +9° and its 2*S*,5*R*-enantiomer, (-)-**2** had mp 91-92° C, $[\alpha]_D$ -9°.
15. H. L. Goering, J. N. Eikenberry, G. S. Koermer and C. J. Lattimer, J. Am. Chem. Soc., **96**, 1493 (1974).

(Received in USA 11 July 1988)