Bioorganic & Medicinal Chemistry Letters, Vol. 1, No. 1, pp. 39-42, 1991
Printed in Great Britain

0960-894X/91 $3.00 + .00

THE SYNTHESIS AND STRUCTURAL CHARACTERIZATION OF WAY-120,491; A NOVEL POTASSIUM CHANNEL ACTIVATOR

Dominick A. Quagliato†*, Leslie G. Humber†, Betsy L. Joslyn†, Richard M. Soll†*, Eric N. C. Browne≠, Chia-cheng Shaw≠, and Donna Van Engen#

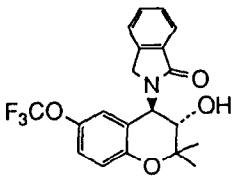
Department of Medicinal Chemistry, Wyeth-Ayerst Research, CN-8000, Princeton, NJ 08543-8000; Chemical Development Division, St. Laurent, Quebec, Canada; and Department of Chemistry, Princeton University, Princeton, NJ 08540

† Department of Medicinal Chemistry; ≠ Chemical Development Division; # Princeton University

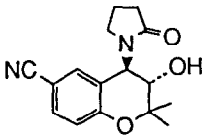
(*Received* 17 *December* 1990)

Abstract: The synthesis of the antihypertensive potassium channel activator WAY-120,491 (**1**) is described. X-ray crystallographic analysis of carbamate **15a** established the 3S,4R configuration of **1**. The large scale classical resolution of racemic **9** was facilitated using authentic seed crystals, whose preparation was accomplished via novel coupling of racemic azidoalcohol **17** with the putative acyltriflate **20**.

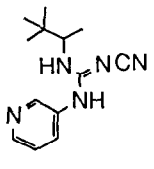
Potassium channel activators comprise an increasing number of structurally diverse compounds whose common pharmacological property involves the ability to enhance cellular potassium efflux and to effect consequent hyperpolarization of the cellular membrane.[1] WAY-120,491 (**1**), currently in clinical trials as an antihypertensive agent, is a variant of the benzopyran class of potassium channel activators.[2] It is structurally distinguished relative to the prototypical benzopyran cromakalim (**2**) by the bulky C-4 isoindolone nucleus and by the moderately electron withdrawing trifluoromethoxy moeity at C-6. In striking contrast to either **2** or the N-cyananoguanidine pinacidil (**3**) at equihypotensive doses in the spontaneously hypertensive rat, **1** produces *both* (a) a slower onset to maximum blood pressure lowering (4 h to peak effect) and (b) persistent antihypertensive activity (>24 h),[2a] two desirable qualities which may show positive clinical benefits with respect to unwanted side effects typically seen with classical peripheral vasodilator agents.[1c] We describe herein the synthesis and structural characterization of WAY-120,491.



AY-32,400 (racemic)
WAY-120,491 (3S,4R)
1



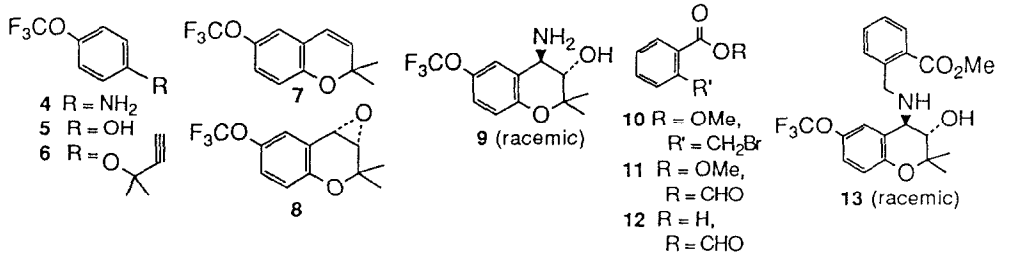
cromakalim
2



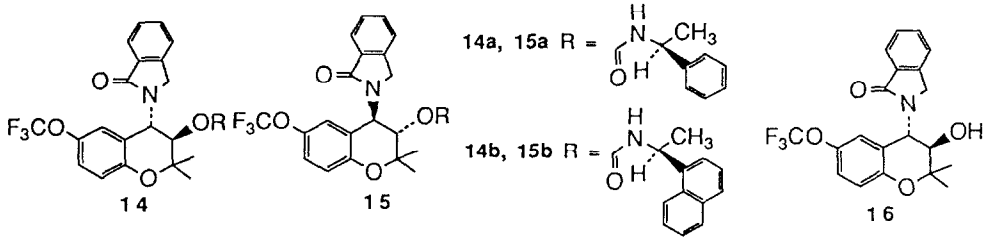
pinacidil
3

The synthesis of racemic **1** (AY-32,400; mp 212 - 213 °C) begins with p-trifluoromethoxyaniline (**4**), which was converted to chromene **7** (bp 50 - 52 °C / 0.5 mmHg) in 58% yield by a sequence analogous to **2**[3]: (1) phenol formation ((a) $NaNO_2$; 0 °C, H_2SO_4; (b) 9 N H_2SO_4, 105 - 110 °C); (2) alkylation of **5** with 3-chloro-3-methyl-1-

butyne[4] (K_2CO_3, KI, CH_3CN, 80 °C, 24 h); and (3) thermal cyclization (185 °C (neat),4 5 min). Epoxidation to **8** using a buffered two phase system (MCPBA, CH_2Cl_2, aq. $NaHCO_3$),[5,6] and subsequent ammonical treatment (conc. NH_4OH, EtOH, 25 °C, 4 days) provided **9** in 52% yield (mp 105 - 106 °C). Isoindolone formation was initially fashioned using **10**[7] (K_2CO_3, CH_3CN, Δ; 48% yield) or in 95% yield by reductive amination[8] with **11**[9] using the reagent derived from $NaBH_3CN$ / $ZnCl_2$ (2 : 1) in MeOH at 50 °C for 14 h.. Using the latter reagent, but at shorter reaction time and lower temperature, aminoester **13** was isolated; cyclization was conveniently effected by heating in toluene.



Three successful routes to the resolution of racemic **1** were examined concurrently. In the first approach, racemic **1** was derivatized as diastereomeric carbamates **14** and **15** by heating the racemic alcohol with either (S)-(-)-α-methylbenzyl isocyanate[10] or (S)-(+)-1-(1-naphthyl)ethyl isocyanate. On multigram scale it was more efficient to separate carbamates **14b** ($[\alpha]_D$ +2.0° (c 1, $CHCl_3$)) and **15b** ($[\alpha]_D$ -38.5° (c 1, $CHCl_3$)) by either flash chromatography[11] or HPLC;[12] carbamates **14a** ($[\alpha]_D$ -4.3° (c 1, $CHCl_3$)) and **15a** ($[\alpha]_D$ -71.2° (c 1, $CHCl_3$)) were isolated similiarly. Trichlorosilane cleavage[13] of carbamates **14** and **15** provided WAY-120,491 (**1**; mp 172 - 172 5 °C; $[\alpha]_D$ -59.9° (c 1, $CHCl_3$)) and its optical anitpode WAY-120,490 (**16**; mp 170 - 171 °C; $[\alpha]_D$ +58.5° (c 1, $CHCl_3$)), respectively, in 75 - 90% yields. X-ray crystallographic analysis of **15a**[14] established the absolute configuration of WAY-120,491 as 3S,4R (Figure 1).

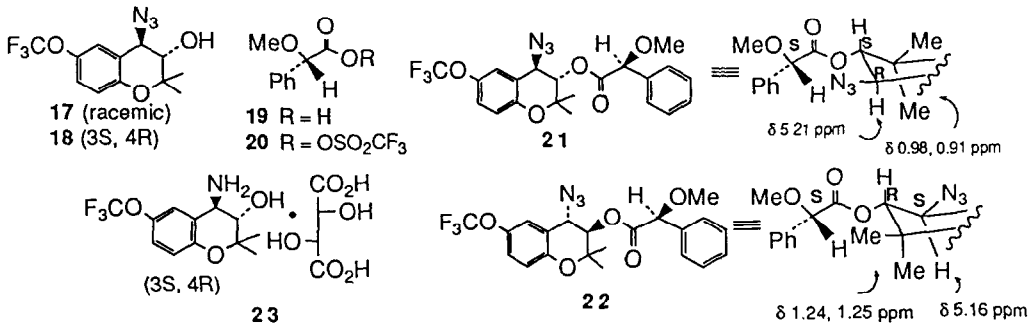


Two alternative resolutions targeted aminoalcohol **9**. Inital success of a classical resolution via chiral salt formation was found to be dependent upon the presence of authentic seed crystals, which were prepared as follows. Epoxide **8** was converted in 82% yield to racemic azidoalcohol **17**, mp 54 - 55 °C, and then coupled to (S)-(+)-α-methoxyphenylacetic acid in a novel fashion via the putative acyltriflate **20**[15] to give **21** (mp 108 - 109 °C, $[\alpha]_D$ +90.0° (c 6.1, MeOH)) and **22** (mp 66 - 68 °C; $[\alpha]_D$ +23.1° (c 5.4, MeOH)) in 88% yield [16] No loss in the

stereochemical integrity of the chiral auxiliary by either ketene formation or racemization was seen under these conditions. Stereochemical assignments were made on the basis of the Trost model.[17] Thus, the *gem* dimethyl groups of **21** appear upfield in the 200 MHz nmr spectrum relative to **22**; similarly, the C-4 proton of **22** appears upfield in comparison to **21**. Ester **21** was advanced to tartrate salt **23** (mp 195 - 195.5 °C; $[\alpha]_D$ +14° (c 1, MeOH)) by: (1) hydrolysis (aq. NaOH, THF, 25 °C, 2 h); (2) catalytic hydrogenation (H_2, 10% Pd/C, MeOH; 66% yield); and (3) salt formation (L-tartaric acid (1.0 equiv).[18]

Racemic **9** was then resolved[19] (L-tartaric acid, EtOH) in 91% yield (>99.9% ee)[18] and converted directly to WAY-120,491 (**1**) in 93% yield by reductive amination / cyclization with **12** ((1) NEt_3, MeOH; (2) $NaBH_4$, 0 °C; (3) HOAc, 60 °C 4 h). This process is quite satisfactory for kilogram production of **1**.

The pharmacolgocial profile of **1** coupled with its synthetic accessibility has made this compound worthy of further development.



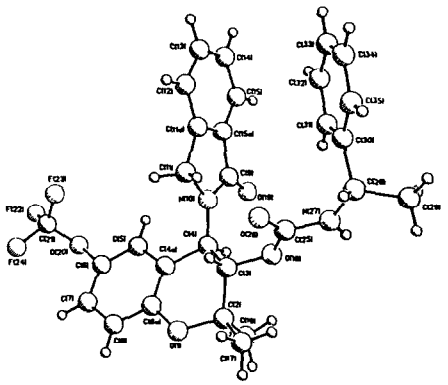


Figure 1. X-ray structure of **15a**.

Acknowledgements. We wish to acknowledge the efforts of Mary Conklin and Ralph Russo in establishing the analytical HPLC determinations. We also acknowledge the scale-up efforts of Mark Lankau, Razzak Noureldin, and Gregory Gavin.

REFERENCES

1. For timely reviews, see: (a) Edwards, G.; Weston, A. H. *Trends in Pharmacological Sciences*, **1990**, (11), 417; (b) Roberson, D. W.; Steinberg, M. I. *J. Med. Chem.* **1990**, 33, 1527; (c) Richer, C.; Pratz, J.; Mulder, P.; Mondot, S ; Giudicelli, J. F.; Cavero, L. *Life Sciences* **1990**, 47, 1693.

2. (a) Morin, M. E.; Wojdan, A.; Oshiro, G.; Colatsky, T.; Quagliato, D. *FASEB J*, **1990**, 4 (3), 2785. (b) Edwards, G.; Weston, A. H.; Oshiro, G. *FASEB J.* **1990**, 4 (3), 2784.

3. Evans, J. M.; Fake, C. S.; Hamilton, T. C.; Poyser, R. H.; Showell, G. A. *J. Med. Chem* **1984**, 27, 1127.

4. Hennion, G. F.; Boisselle, A. P. *J. Org. Chem.* **1961**, 26, 725.

5. Anderson, W. K.; Veysoglu, T.; *J. Org. Chem.* **1973**, 38, 2267.

6. Significant acid catalyzed epoxide opening occurs in the absence of buffer; however, MCPBA without buffer has been used recently with severely electron deficient chromenes: Bergmann, R.; Gericke, R *J Med Chem.* **1990**, 33, 492.

7. Hellwinkel, D.; Siegbert, B. *Chem. Ber.* **1987**, 120, 1151.

8. Kim, S. H.; Oh, C. H.; Ko, J. S.. Ahn, K. H.; Kim, Y. J. *J. Org. Chem.*, **1985**, 50, 1927.

9. Modification of Brown, C.; Sargent, M. V. *J. Chem. Soc. C*, **1969**, 1818.

10. (a) Buckle, D. R.; Arch, J. R. S.; Fenwick, A. E.; Houge-Frydrych, C. S. V.; Pinto, I. L.; Smith, D. G., Taylor, S. G.; Tedder, J. M. *J. Med. Chem.* **1990**, 33, 3028. (b) Ashwood, V. A.; Buckingham, R. E.; Cassidy, F.; Evans, J. E.; Fauk, E. A.; Hamilton, T. C.; Nash, D. J.; Stemp, G.; Willcocks, K. *J. Med Chem* **1986**, 29, 2194.

11. Still, W. C.; Kahn, M.; Mita, A. *J. Org. Chem.* **1978**, 43, 2923.

12. HPLC separations were performed using a Rainin Dynamax column (21.4 and 41.4 mmID) packed with 60 A 8 μM silica gel and eluting with CH_2Cl_2 / hexane / ethyl acetate (6 / 6 /1).

13. Pirkle, W. H.; Hauske, J. R. *J. Org. Chem* **1977**, 42, 2781.

14. *Crystal data* for **15a**: $C_{29}H_{27}F_3N_2O_5$, FW = 540.6, monoclinic, a = 12.689 (5) Å, b = 19.192 (7) Å, c = 12.372 (4) Å, $\alpha = 90.0^{\circ}$, $\beta = 114.26\ (3)^{\circ}$, $\gamma = 90.0^{\circ}$, V = 2747 (2) $Å^3$, space group $P2_1/c$, Z = 4, D_c = 1.31 g cm^{-3}, CuKα radiation (λ = 1.5418 Å), $3^{\circ} \leq 2\theta \leq 114^{\circ}$, unique data = 3699, observed data = 2882, $F_o > 3\ \sigma\ (F_o)$. The structure was resolved by direct methods (SHELXTL). Carbon, nitrogen, and oxygen were refined anisotropically, fluorine was refined isotropically; the trifluoromethyl group is disordered; all hydrogen atoms were included at idealized positions. Refinement converged at R = 0.069, R_w = 0.076.

15. For an example of an aryl acyltriflate preparation and coupling, see: Koreeda, M.; Brown, L. *J. Org. Chem.* **1984**, 49, 3875.

16. At 0 °C to **19** (0.34 mol in CH_2Cl_2 (900 mL) containing pyridine (0.93 mol) was added slowly trifluoromethanesulfonic anhydride (0.34 mol). After 10 min, a solution of **17** (0.23 mol) in CH_2Cl_2 (150 mL) was added dropwise. The cold bath was removed and stirring was continued for 60 min. The reaction reaction mixture was quenched with sat. $NaHCO_3$ and extracted into ether. The organic phase was washed successively with aq. $CuSO_4$ and sat. $NaHCO_3$, dried ($MgSO_4$)., and concentrated to give 98.4 g (88% yield) of crude product. Pure ester **21** was isolated by trituration with hexane. Pure **22** is obtained by HPLC separation using 2% *t*-BuOMe / hexane elution.

17. Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, 51, 2370.

18. The enantiomeric purity of **23** was determined as the benzamide derivative by HPLC using a Chiracel OD column with 7% isopropanol / hexane eluiton.

19. This resolution with L-tartartic acid, as well as other classical chiral resolving acids, initailly failed in the absence of authentic seed crystals.