Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 2483–2493

TETRAHEDRON: *ASYMMETRY*

Reaction between hydrazines and chiral α-acetylenic ketones: synthesis of novel enantiomerically pure pyrazolyl-β-amino alcohols†

Gemma Cabarrocas,[a] Montserrat Ventura,[a] Miguel Maestro,[b] José Mahía[b] and José M. Villalgordo[a,*]

[a]*Departament de Química, Facultat de Ciències, Universitat de Girona, Campus de Montilivi, E-17071 Girona, Spain*
[b]*Servicios Xerais de Apoio á Investigación, Universidade da Coruña, Campus da Zapateira s/n, E-15071 A Coruña, Spain*

Received 13 April 2000; accepted 23 May 2000

Abstract

A simple and efficient methodology toward the stereoselective synthesis of novel, enantiomerically pure, pyrazolyl-β-amino alcohols is presented. Thus, when hydrazines **4a**,**b** were allowed to react at 0°C with chiral α-acetylenic ketones of type **3**, pyrazolyl oxazolidine derivatives **5a**–**d** were formed with total regioselectivity in 92–97% yield. Subsequent oxazolidine ring opening by means of TFA, and re-protection of the amino group as the *N*-Boc derivatives, afforded enantiopure amino alcohols **7a**–**d**. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

The stereoselective synthesis of β-amino alcohols is a topic of current interest. In recent years, members of this group of compounds have been used in pharmacological applications such as modulators of the potassium channel in cells[1] or as a core moieties of a number of biologically important compounds.[2–5] In addition, β-amino alcohols bearing heterocyclic residues are of particular interest, since they can serve as novel building-blocks for biologically active molecules.[6–10]

On the other hand, it is well known that enantiomerically pure β-amino alcohols are finding extensive use in asymmetric synthesis.[11,12] They are frequently used as chiral synthons,[13] and as precursors of chiral auxiliaries.[14–16] They have been used as well as efficient chiral ligands in many asymmetric reactions involving achiral reagents such as Lewis acids,[17,18] organometallic reagents[19] or metallic hydrides.[20,21] In this particular field, it is often possible to achieve high levels of asymmetric induction by modulating the steric and electronic properties of the intervening

* Corresponding author. Fax +34-972418150; e-mail: dqjvs@xamba.udg.es
† Taken in part from the PhD Thesis of G.C. (Universitat de Girona, 1999).

0957-4166/00/$ - see front matter © 2000 Elsevier Science Ltd. All rights reserved.
PII: S0957-4166(00)00204-4

chiral ligands. In this sense, there is a constant need for the development of new synthetic repertoires toward the preparation of novel enantiopure ligands.

Despite the numerous synthetic methods available for the preparation of chiral 1,2-amino alcohols, only a few stereoselective preparations have been reported.[22] The most direct synthesis of optically active 1,2-amino alcohols is the reduction of α-amino acids;[23–26] however, this method is limited by the nature of lateral chains.

On the other hand, α-acetylenic ketones of type **1** have been shown to be highly versatile building blocks. These conjugated ynones have proven to be very suitable substrates for the synthesis of a wide range of heterocyclic systems.[27–34] In addition, when properly functionalised, compounds of type **1** have also proven to be valuable substrates for the combinatorial and parallel synthesis on solid support of highly molecular diverse 2,4,6-trisubstituted pyrimidines.[35,36] In view of the strong synthetic potential of these conjugated ynones **1**, we recently described[37] a very efficient and straightforward synthesis of novel chiral α-acetylenic ketones of type **3** (Fig. 1). These compounds bear a protected β-amino alcohol functionality as a special structural feature. This chiral moiety should be readily incorporated into a variety of relevant core structures.

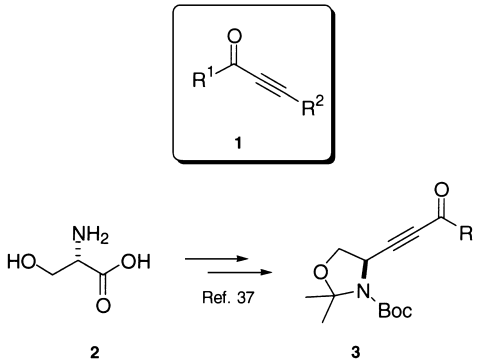


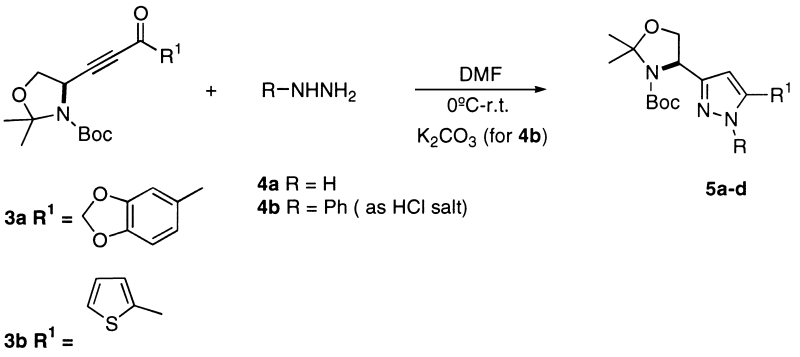
Figure 1.

With the aim of validating our working hypothesis and in order to check the utility of such chiral building blocks **3** for the preparation of novel optically active 1,2-amino alcohols containing heterocyclic residues on the lateral chain, we focused our interest on the pyrazole nucleus.

2. Results and discussion

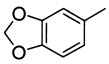
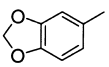
When hydrazine **4a** or phenyl hydrazine hydrochloride **4b** were allowed to react in DMF (in the presence of K_2CO_3 for **4b**) at 0°C with chiral ynones **3a–b** for a period of 16–22 h, the corresponding pyrazolyl oxazolidines **5a–d** were isolated almost quantitatively (92–97% yields). In marked contrast with a previous report,[38] under our reaction conditions, only one regioisomer **5c–d** was detected (Scheme 1, Table 1). Although under these reaction conditions we did not expect that the stereogenic centre at the oxazolidine ring could be affected,‡ we checked the

‡ In another set of experiments using chiral conjugated ynones of type **3**, their cyclocondensation reaction with other more basic bidentated nucleophiles (e.g. amidines) produced the expected compounds (e.g pyrimidines) but with high levels of epimerisation.[39]



Scheme 1.

Table 1
Prepared pyrazolyl oxazolidine derivatives **5a–d**

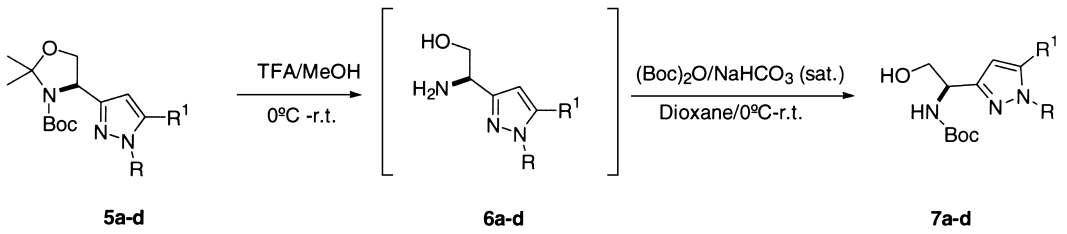
Entry	R	R^1	Compound	Yield (%)[a]	m.p. (°C)	$[\alpha]_D^{20}$ in MeOH
1	H		**5a**	97	oil	-97.9 (c=2.15)
2	H		**5b**	93	135-136	-125.5 (c=0.80)
3	Ph		**5c**	92	oil	-69.2 (c=1.89)
4	Ph		**5d**	96	oil	-82.9 (c=1.73)

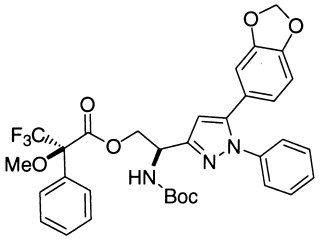
[a] Yields of isolated pure products

enantiomeric excess of the recovered pyrazoles **5** and these were found to be enantiomerically pure (≥95%, ^{1}H NMR analysis, 200 MHz in the presence of varying amounts of Eu(hfc)$_3$).

Next, treatment of **5a–d** with TFA in MeOH at 0°C afforded the corresponding amino alcohol derivatives **6a–d** that were not isolated, but re-protected in situ leading to *N*-Boc protected chiral β-amino alcohol derivatives **7a–d** in good overall yields. Again, in the case of **7c** the corresponding Mosher's ester derivative **8** was prepared from the crude reaction mixture and the enantiomeric excess of this derivative assessed by ^{1}H NMR and found to be diastereoisomerically pure (Scheme 2, Table 2).

In addition, also for **7c**, we were able to grow crystals that were suitable for an X-ray crystal structure determination that on one side confirmed the structure of the proposed regioisomer and additionally that the crystals were enantiomerically pure. It was then assumed that they had the expected absolute configuration. This assumption was extended to the complete series of synthesised compounds **7a–d** (Fig. 2).

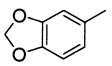
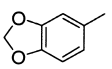




8

Scheme 2.

Table 2
Prepared chiral pyrazolyl 1,2-amino alcohols **7a–d**

Entry	R	R^1	Compound	Yield (%)[a]	m.p. (°C)	$[\alpha]_D^{20}$ in MeOH
1	H		**7a**	62	142-143	-36.6 (c=1.54)
2	H		**7b**	91	75-76	-74.7 (c=0.58)
3	Ph		**7c**	65	108-109	-71.6 (c=0.57)
4	Ph		**7d**	83	oil	-46.9 (c=0.55)

[a] Overall yields (two steps) of isolated pure products

In summary, we have developed a short and efficient procedure for the stereoselective synthesis of novel optically active pyrazolyl-1,2-amino alcohols. The key step in this strategy was the total regioselectivity exhibited by conjugated ynones **3a–b** in their tandem Michael addition–cyclocondensation reaction with hydrazines **4a–b** under the very mild conditions employed. The obtained pyrazolyl amino alcohols can serve as useful ligands in a variety of asymmetric trans-

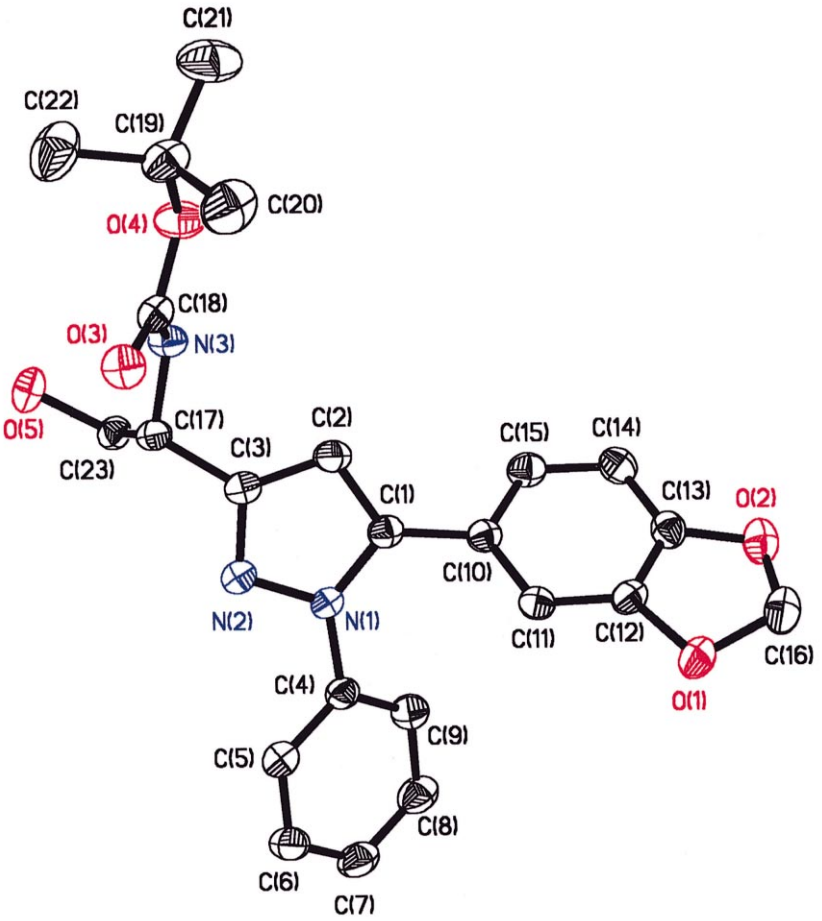


Figure 2. Ortep plot[40] of the molecular structure of **7c** with 50% probability ellipsoids

formations. Their further elaboration into chiral oxazolines and their application in asymmetric synthesis is the subject of current efforts in our laboratory and the results will be published in due course.

3. Experimental

3.1. General methods

All commercially available chemicals were used as purchased. Melting points (capillary tube) were measured with a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Mattson–Galaxy Satellite FT-IR. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, on a Bruker DPX200 Advance instrument with TMS as internal standard. MS spectra were recorded on a VG Quattro instrument in the positive ionisation FAB mode, using 3-NBA or 1-thioglycerol as the matrix. Elemental analyses were performed on an apparatus from

Thermo instruments, model EA1110-CHNS. Optical rotation measurements were performed on a Perkin–Elmer 241 polarimeter. Analytical TLC was performed on precoated TLC plates, silica gel 60 F_{254} (Merck). Flash-chromatography purifications were performed on silica gel 60 (230–400 mesh, Merck).

3.2. *Synthesis of pyrazolyl oxazoline derivatives **5a–d**. General procedure*

To a cooled (0°C) solution of acetylenic ketones **3a–b** (300 mg) in DMF (2.5 mL), 1.1 equiv. of aqueous hydrazine **4a** were added. Alternatively, addition of phenyl hydrazine hydrochloride **4b** was followed by addition of 1.3 equiv. of K_2CO_3. The reaction mixture was stirred at 0°C for 2 h and 16–18 h at rt (TLC monitoring). DMF was eliminated under reduced pressure, and the residue partitioned between CH_2Cl_2 (15 mL) and H_2O (10 mL). The layers were separated, and the aqueous one extracted with CH_2Cl_2 (2×15 mL). The combined organic layers were dried over $MgSO_4$. The solvent was evaporated and the resulting residue purified by flash-chromatography (hexanes/AcOEt as eluent) to afford pure **5a–d** (Table 1).

3.3. tert-*Butyl (4*R*)-4-[5-(1,3-benzodioxol-5-yl)-1*H*-3-pyrazolyl]-2,2-dimethyl-1,3-oxazolane-3-carboxylate **5a***

According to the general procedure described in Section 3.2, reaction between **3a** and **4a** afforded 302 mg (97%) of **5a** as a colourless oil. $[\alpha]_D^{20}$ –97.9 (*c* 2.15, MeOH). IR (film, *v*): 3400 br., 3289 m, 3144 w, 2973 m, 2958 m, 2925 m, 2876 m, 2780 w, 1697s, 1611 w, 1575 w, 1496 m, 1464 m, 1385 m, 1237 m, 1170 m, 1100 m, 1041 m, 976 w, 937 m, 851 m, 809 m, 771 w, 724 w. ^{1}H NMR (DMSO-d_6, T=60°C), δ=12.65 (s, br., 1H, NH), 7.4–7.25 (m, 2H, C*H* arom.), 7.01 (d, J=8.0 Hz, 1H, C*H* arom.), 6.47 (s, 1H, C*H* arom.), 6.11 (s, 2H, OCH_2O), 5.05 (dd, J=6.4 Hz, J′=3.0 Hz, 1H, C*H*), 4.31 (dd, J=8.8 Hz, J′=6.4 Hz, 1H, syst. AB, CH_2O), 4.06 (dd, J=8.8 Hz, J′=3.0 Hz, 1H, syst. AB, CH_2O), 1.74 (s, 3H, C(CH_3)$_2$), 1.63 (s, 3H, C(CH_3)$_2$), 1.44 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (DMSO-d_6, T=60°C), δ=151.1 (s, N*C*O), 150.0, 147.5, 146.6, 145.3, 125.4 (5s, C arom.), 118.6, 108.2, 105.3 (3d, CH arom.), 100.7, (t, O*C*H$_2$O), 99.0 (d, CH arom.), 93.2 (s, *C*(CH$_3$)$_2$), 78.8 (s, *C*(CH$_3$)$_3$), 68.3 (t, CH$_2$O), 54.2 (d, CH), 27.7 (q, C(*C*H$_3$)$_3$), 25.9 (q, C(*C*H$_3$)$_2$), 23.9 (q, C(*C*H$_3$)$_2$). MS (FAB$^+$) *m*/*e*: 388 ([M+1], 100), 387 (M$^+$, 93), 332 (51), 274 (60), 272 (54), 231 (50), 230 (79). Anal. calcd for $C_{20}H_{25}N_3O_5$ (387.43): C, 62.00%; H, 6.50%; N, 10.85%. Found: C, 62.30%; H, 6.26%; N, 10.74%.

3.4. tert-*Butyl (4*R*)-2,2-dimethyl-4-[5-(2-thienyl)-1*H*-3-pyrazolyl]-1,3-oxazolane-3-carboxylate **5b***

According to the general procedure described in Section 3.2, reaction between **3b** and **4a** afforded 290 mg (93%) of **5b** as a colourless solid. M.p. 135–136°C. $[\alpha]_D^{20}$ –125.5 (*c* 0.80, MeOH). IR (KBr, *v*): 3450 br., 3282 m, 3156 w, 2983 m, 2935 w, 2873 w, 1660 s, 1579 w, 1473 w, 1456 w, 1407 m, 1366 m, 1258 m, 1202 w, 1167 m, 1137 m, 1100 m, 1063 m, 946 w, 919 w, 848 m, 809 w, 791 w, 732 w, 701 w. ^{1}H NMR (DMSO-d_6, T=60°C), δ=12.65 (s, br. 1H, NH), 7.55–7.4 (m, 2H, CH arom.), 7.2–7.15 (m, 1H, CH arom.), 6.43 (s, 1H, arom.), 5.07 (dd, J=6.3 Hz, J′=2.8 Hz, 1H, C*H*), 4.32 (dd, J=8.8 Hz, J′=6.3 Hz, 1H, Sist. AB, CH_2O), 4.06 (dd, J=8.8 Hz, J′=2.8 Hz, 1H, Sist. AB, CH_2O), 1.74 (s, 3H, C(CH_3)$_2$), 1.63 (s, 3H, C(CH_3)$_2$), 1.45 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (DMSO-d_6, T=60°C), δ=151.0 (s, N*C*O), 127.3 (d, CH arom.) 127.2 (s, C arom.), 124.4 (d, CH

arom.), 124.3 (s, C arom.), 123.3 (d, CH arom.), 123.2 (s, C arom.), 99.5 (d, CH arom.), 93.2 (s, $C(CH_3)_2$), 79.0 (s, $C(CH_3)_3$), 68.2 (t, CH_2O), 53.6 (d, CH), 27.7 (q, $C(CH_3)_2$), 26.0 (q, $C(CH_3)_2$), 23.8 (q, $C(CH_3)_3$). MS (FAB$^+$) *m/e*: 351 ([M+2]$^+$, 11), 350 ([M+1]$^+$, 45), 349 (M$^+$, 40), 294 (57), 250 (66), 236 (96), 193 (63), 192 (100). Anal. calcd for $C_{17}H_{23}N_3O_3S$ (349.44): C, 58.43%; H, 6.63%; N, 12.02%; S, 9.17%. Found: C, 58.38%; H, 6.55%; N, 12.02%; S, 8.91%.

3.5. tert-*Butyl (4*R*)-4-[5-(1,3-benzodioxol-5-yl)-1-phenyl-1*H*-3-pyrazolyl]-2,2-dimethyl-1,3-oxazolane-3-carboxylate* **5c**

According to the general procedure described in Section 3.2, reaction between **3a** and **4b** afforded 342 mg (92%) of **5c** as a yellowish oil. $[\alpha]_D^{20}$ –69.2 (*c* 1.89 MeOH). IR (KBr, *ν*): 2975 m, 2928 m, 2875 m, 1697 s, 1598 m, 1503 m, 1487 m, 1457 m, 1382 m, 1236 m, 1171 m, 1134 w, 1095 m, 1040 m, 936 m, 852 m, 809 m, 766 m, 695 m. ^{1}H NMR (DMSO-d_6, $T=60°C$), $\delta=7.50$–7.35 (m, 5H, CH arom.) 7.0–6.80 (m, 3H, CH arom.), 6.48 (s, 1H, CH arom.), 6.11 (s, 2H, OCH_2O), 5.10 (dd, J = 6.3 Hz, J′ = 3.0 Hz, 1H, CH), 4.36 (dd, J = 8.7 Hz, J′ = 6.3 Hz, 1H sist. AB, CH_2O), 4.15 (dd, J = 8.7 Hz, J′ = 3.0 Hz, 1H, sist. AB, CH_2O), 1.75 (s, 3H, $C(CH_3)_2$), 1.65 (s, 3H, $C(CH_3)_2$), 1.46 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (DMSO-d_6, $T=60°C$), $\delta=153.3$ (s, C arom.), 151, (s, NCO), 147.1, 147.0, 142.6, 139.6 (4 s, C arom.), 128.5, 126.9, 124.5 (3d, CH arom.), 123.6 (s, C arom.), 122.2, 108.3, 108.0, 105.0 (4d, CH arom.), 101.0 (t, OCH_2O), 93.2 (s, $C(CH_3)_2$), 78.8 (s, $C(CH_3)_3$), 68.3 (t, CH_2O), 55.0 (d, CH), 27.7 (q, $C(CH_3)_3$), 25.8, 23.9 (2 q, $C(CH_3)_2$). MS (FAB$^+$) *m/e*: 464 ([M+1]$^+$, 100), 463 (M$^+$, 29), 348 (70), 306 (66). Anal. calcd for $C_{26}H_{29}N_3O_5$ (463.53): C, 67.37%; H, 6.31%; N, 9.07%. Found: C, 67.58%; H, 6.42%; N, 9.15%.

3.6. tert-*Butyl (4*R*)-2,2-dimethyl-4-[1-phenyl-5-(2-thienyl)-1*H*-3-pyrazolyl]-1,3-oxazolane-3-carboxylate* **5d**

According to the general procedure described in Section 3.2, reaction between **3b** and **4b** afforded 366 mg (96%) of **5d** as a yellowish oil. $[\alpha]_D^{20}$ –82.96 (*c* 1.73 MeOH). IR (film, *ν*): 3103 w, 3073 w, 2977 m, 2932 m, 2873 m, 1698 s, 1597 m, 1504 m, 1477 w, 1456 m, 1382 m, 1314 w, 1256 m, 1205 w, 1171 m, 1133 w, 1093 m, 1059 m, 926 d, 849 m, 791 d, 766 m, 697 m. ^{1}H NMR (DMSO-d_6, $T=60°C$), $\delta=7.62$ (dd, J = 5.0 Hz, J′ = 1.2 Hz, 1H, CH arom.), 7.6–7.4 (m, 5H, CH arom.), 7.11 (dd, J = 5.0 Hz, J′ = 3.6 Hz, 1H, CH arom.), 7.03 (dd, J = 3.6 Hz, J′ = 1.2 Hz, 1H, CH arom.), 6.60 (s, 1H, CH arom.), 5.09 (dd, J = 6.4 Hz, J′ = 3.0 Hz, 1H, CH), 4.36 (dd, J = 8.7 Hz, J′ = 6.4 Hz, 1H, sist. AB, CH_2O), 4.15 (dd, J = 8.7 Hz, J′ = 3.0 Hz, 1H, sist. AB, CH_2O), 1.75 (s, 3H, $C(CH_3)_2$), 1.65 (s, 3H, $C(CH_3)_2$), 1.47 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (DMSO-d_6, $T=60°C$), $\delta=153.4$ (s, C arom.), 151.0 (s, NCO), 139.3, 136.7, 130.3 (3s, C arom.), 128.7, 127.9, 127.2, 127.1, 127.0, 125.5, 105.1 (5d, CH arom.), 93.2 (s, $C(CH_3)_2$), 78.8 (s, $C(CH_3)_3$), 68.2 (t, CH_2O), 54.9 (d, CH), 27.7 (q, $C(CH_3)_3$), 25.9 (q, $C(CH_3)_2$), 23.9 (q, $C(CH_3)_2$). MS (FAB$^+$) *m/e*: 427 ([M+2]$^+$, 29), 426 ([M+1]$^+$, 100), 425 (M$^+$, 20), 370 (41), 326 (44), 312 (60), 310 (98), 269 (70), 268 (96). Anal. calcd for $C_{23}H_{27}N_3O_3S$ (425.54): C, 64.92%; H, 6.40%; N, 9.87%; S, 7.54%. Found: C, 65.09%; H, 6.22%; N, 9.59%; S, 7.74%.

3.7. Synthesis of pyrazolyl 1,2-aminoalcohol derivatives **7a**–**d***. General procedure*

To a cooled (0°C) solution of pyrazole derivatives **5a**–**d** in MeOH (0.7 mL/mmol), TFA (3 mL/mmol) was added dropwise. After stirring 2 h at 0°C and overnight at rt, TFA was removed

under gentle Ar stream. The resulting residue was re-dissolved in 1:1 mixture dioxane:$NaHCO_3$ (sat.) (12 mL/mmol), cooled to 0°C and 3.3 equiv. of $(Boc)_2O$ added in one portion. The reaction mixture was stirred at 0°C for 4 h and overnight at rt. The mixture was partitioned between H_2O and AcOEt, the organic layer separated and dried over $MgSO_4$ (anh.). Filtration, removal of the solvent and purification of the resulting residue by flash chromatography (hexanes/AcOEt as eluent) afforded pure **7a**–**d** (Table 2).

*3.8. Synthesis of (2*R*)-2-(3-Benzo[*d*][1,3]dioxol-5-yl-1*H*-5-pyrazolyl)-2-[(1,1-dimethylethoxy) carbonylamino]ethan-1-ol **7a***

According to the general procedure described in Section 3.7, reaction of **5a** (267 mg, 0.69 mmol) afforded 149 mg (62%) of **7a** as a colourless solid. M.p. 142–143°C. $[\alpha]_D^{20}$ –36.6 (*c* 1.54, MeOH). IR (KBr, *ν*): 3550 br., 3400 m, 3278 m, 2974 m, 2926 m, 2779 w, 1687 s, 1499 m, 1465 m, 1392 m, 1367 m, 1331 w, 1241 s, 1167 m, 1108 w, 1038 m, 976 w, 934 m, 875 m, 859 m, 809 m, 728 w, 606 w. ^{1}H NMR (DMSO-d_6), δ = 13.10–12.40 (s, br., 1H, NH), 7.35–6.95 (m, 4H, 3 CH arom.+CON*H*), 6.54 (s, 1H, CH arom.), 6.13 (s, 2H, O*C*H_2O), 4.9 (s, br., 1H, OH), 4.75–4.65 (m, 1H, CH), 3.70–3.50 (m, 2H, *C*H_2OH), 1.49 (s, 9H, C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$), δ = 156.1 (s, C arom.), 149.1 (s, NCO), 147.9, 147.6, 146.8, 124.9 (4s, C arom.), 119.3, 108.5, 106.2 (3d, CH arom.), 101.1 (t, OCH_2O), 100.5 (d, CH arom.), 80.1 (s, *C*(CH_3)$_3$), 64.8 (t, CH_2OH), 50.2 (d, CH), 28.3 (q, C(*C*H_3)$_3$).). MS (FAB$^+$) *m*/*e*: 348 ([M+1]$^+$, 66), 347 (M$^+$, 48), 292 (74), 231 (100), 216 (50). Anal. calcd for $C_{17}H_{21}N_3O_5$ (347.37): C, 58.68%; H, 6.09%; N, 12.10. Found: C, 58.68%; H, 6.21%; N, 12.35%.

*3.9. (2*R*)-2-[(1,1-Dimethylethoxy)carbonylamino]-2-[3-(2-thienyl)-1*H*-5-pyrazolyl]ethan-1-ol **7b***

According to the general procedure described in Section 3.7, reaction of **5b** (174 mg, 0.50 mmol) afforded 140 mg (91%) of **7b** as a colourless solid. M.p. 75–76°C. $[\alpha]_D^{20}$ –74.7 (*c* 0.58, MeOH). IR (KBr, *ν*): 3600 br., 3417 s, 2975 m, 2930 m, 2873 w, 1688 s, 1515 m, 1474 w, 1456 w, 1393 m, 1367 m, 1279 w, 1251 m, 1167 m, 1057 m, 1026 m, 925 w, 850 m, 800 w, 698 m. ^{1}H NMR (DMSO-d_6), δ = 1360–11.80 (s, br. 1H, NH), 7.55–6.90 (m, 4H, 3 CH arom.+N*H*CO), 6.51 (s, 1H, CH arom.), 4.90–4.60 (m, 1H, CH), 4.30–3.70 (s, br., OH), 3.66 (d, J = 6.0 Hz, 2H, *C*H_2OH), 1.49 (s, 9H, C(C*H*$_3$)$_3$). ^{13}C NMR ($CDCl_3$), δ = 156.1 (s, C arom.), 148.2 (s, NCO), 142.9, 133.8 (2s, 2 C arom.), 127.6, 125.1, 124.2, 101.2 (4d, 4CH arom.), 80.3 (s, *C*(CH_3)$_3$), 64.8 (t, *C*H_2OH), 49.7 (d, CH), 28.3 (q, C(*C*H_3)$_3$). MS (FAB$^+$) *m*/*e*: 311 ([M+2]$^+$, 10), 310 ([M+1]$^+$, 46), 309 (M$^+$, 44), 254 (87), 193 (100). Anal. calcd for $C_{14}H_{19}N_3O_3S$ (309.39): C, 54.35%; H, 6.19%; N, 13.58; S, 10.36. Found: C, 54.10%; H, 6.08%; N, 13.78%; S, 10.33%.

*3.10. (2*R*)-2-(5-Benzo[*d*][1,3]dioxol-5-yl-1-phenyl-1*H*-3-pyrazolyl)-2-[(1,1-dimethylethoxy)-carbonylamino]ethan-1-ol **7c***

According to the general procedure described in Section 3.7, reaction of **5c** (207 mg, 0.45 mmol) afforded 122 mg (65%) of pure **7c** as a colourless solid. M.p. 108–109°C. $[\alpha]_D^{20}$ –71.6 (*c* 0.57, MeOH). IR (KBr, *ν*): 3500 br., 3368 m, 3276 m, 3063 w, 2979 w, 2931 w, 2884 w, 2764 w, 1668 s, 1600 w, 1541 m, 1503 s, 1485 m, 1455 m, 1369 m, 1337 m, 1293 m, 1275 m, 1235 m, 1170 m, 1103 w, 1057 m, 1037 m, 981 w, 932 m, 882 w, 860 w, 809 m, 757 m, 693 m, 632 w. ^{1}H NMR ($CDCl_3$), δ = 7.40–7.25 (m, 5H, CH arom.), 6.80–6.55 (m, 3H, CH arom.), 6.45 (s, 1H, CH

arom.), 5.99 (s, 2H, OCH_2O), 5.57 (s, br., 1H, NH), 5.10–4.90 (m, 1H, CH), 4.12 (dd, J = 11.2 Hz, J′ = 4.4 Hz, 1H, CH_2O), 3.96 (dd, J = 11.2 Hz, J′ = 4.2 Hz, 1H, CH_2O), 2.50–1.90 (s, br., 1H, OH), 1.51 (s, 9H, C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$), δ = 156.0 (s, C=N), 151.8 (s, NCO), 147.8, 147.7, 143.8, 139.7 (4s, C arom.), 128.9, 127.6, 125.1 (3d, CH arom.), 123.9 (s, C arom.), 122.8, 109.1, 108.4, 106.3 (4d, CH arom.), 101.3 (t, OCH_2O), 79.8 (s, *C*(CH_3)$_3$), 65.9 (t, *C*H_2O), 50.7 (d, CH), 28.4 (q, C(*C*H_3)$_3$). MS (FAB$^+$) *m*/*e*: 424 ([M+1]$^+$, 71), 423 (M$^+$, 10), 369 (52), 336 (26), 307 (100), 292 (69). Anal. calcd for $C_{23}H_{25}N_3O_5$ (423.46): C, 62.24%; H, 5.95%; N, 9.92. Found: C, 62.02%; H, 6.22%; N, 10.06%.

*3.11. (2*R*)-2-[(1,1-Dimethylethoxy)carbonylamino]-2-[1-phenyl-5-(2-thienyl)-1*H*-3-pyrazolyl]-ethan-1-ol **7d***

According to the general procedure described in Section 3.7, reaction of **5d** (286 mg, 0.67 mmol) afforded 215 mg (83%) of pure **7d** as a yellowish oil. $[\alpha]_D^{20}$ –46.9 (*c* 0.55, MeOH). IR (film, *v*): 3500 br., 3423 m, 3103 w, 3071 w, 2972 m, 2926 m, 2871 m, 2857 m, 1706 s, 1597 m, 1501 s, 1455 m, 1369 m, 1323 w, 1275 m, 1249 m, 1166 s, 1055 m, 1024 m, 964 w, 929 m, 851 m, 794 w, 766 m, 697 m. ^{1}H NMR ($CDCl_3$), δ = 7.45–7.35 (m 5H, CH arom.), 7.32 (dd, J = 5.2 Hz, J′ = 1.2 Hz, 1H, CH arom.), 6.97 (dd, J = 5.2 Hz, J′ = 3.6 Hz, 1H, CH arom.), 6.85 (dd, J = 3.6 Hz, J′ = 1.2 Hz, 1H, CH arom.), 6.58 (s, 1H, CH arom.), 5.55 (s, br., 1H, NH), 5.10-4.90 (m, 1H, CH), 4.12 (dd, J = 11.2 Hz, J′ = 4.2 Hz, 1H, CH_2O), 2.40–1.80 (s, br., 1H, OH), 1.51 (s, 9H, C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$), δ = 156.0 (s, C=N), 151.8 (s, NCO), 139.5, 137.9, 130.9 (3s, C arom.), 129.0, 128.4, 127.4, 127.3, 126.7, 126.1, 106.5 (7d, CH arom.), 79.8 (s, *C*(CH_3)$_3$), 65.8 (t, *C*H_2O), 50.7 (d, CH), 28.3 (q, C(*C*H_3)$_3$). MS (FAB$^+$) *m*/*e*: 387 ([M+2]$^+$, 25), 386 ([M+1]$^+$, 97), 385 (M$^+$, 4), 354 (22), 330 (69), 298 (25), 269 (100), 254 (59). Anal. calcd for $C_{20}H_{23}N_3O_3S$ (385.48): C, 62.32%; H, 6.01%; N, 10.90; S, 8.32%. Found: C, 62.54%; H, 6.18%; N, 11.07%; S, 8.08%.

*3.12. Synthesis of the Mosher's ester derivative **8***

To a solution of the amino alcohol derivative **7c** (25 mg, 0.058 mmol) in anhydrous CCl_4 (0.29 mL), dry pyridine (0.17 mL) was added. After stirring for 5 min until homogenisation, (R)-(–)-MPTA–Cl (15.2 μL, 0.082 mmol) was added. The reaction mixture was stirred at rt under N_2 for 1 h. The mixture was diluted with CH_2Cl_2, and washed successively with sat. $NaHCO_3$ and brine. The organic layer dried over $MgSO_4$, and filtered and the solvent eliminated under reduced pressure to afford quantitatively **8** which was dried under H.V. and analysed without further purification. IR (KBr, *v*): 3362 br., 3064 w, 2956 m, 2923 m, 2853 m, 1751 s, 1712 s, 1599 m, 1500 s, 1487 s, 1454 m, 1371 m, 1333 w, 1238 s, 1167 s, 1123 m, 1078 w, 1035 w, 935 w, 864 w, 806 m, 765 m, 721 m, 697 m. ^{1}H NMR ($CDCl_3$), δ = 8.65 (s, br., 1H, N*H*CO), 7.60–7.25 (m, 10H, CH arom.), 6.80–6.60 (m, 3H, CH arom.), 6.29 (s, 1H, CH arom.), 6.0 (s, 2H, OCH_2O), 5.25 (s, br., 1H, CH), 4.80–4.65 (m, 2H, CH_2O), 3.52 (s, 3H, OCH_3), 1.49 (s, 9H, C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$), δ = 166.3 (s, CO), 155.1 (s, C=N), 149.9 (s, NCO), 149.7 (s, C arom.), 147.8, 147.6, 143.8, 139.8, 132.1 (1s, C arom.+CF_3), 129.5, 128.9, 128.3, 127.6, 127.4, 125.1 (6s, CH arom.), 123.9 (s, C arom.), 122.8, 109.0, 108.4, 105.9 (4d, CH arom.), 101.3 (t, OCH_2O), 79.9 (s, *C*(CH_3)$_3$), 67.4 (t, CH_2O), 55.4 (q, OCH_3), 48.3 (d, CH), 28.32 (q, C(*C*H_3)$_3$). Anal. calcd for $C_{33}H_{32}F_3N_3O_7$ (639.62): C, 61.97%; H, 5.04%; N, 6.57. Found: C, 62.26%; H, 5.28.18%; N, 6.29%.

Acknowledgements

Generous financial support from the Dirección General de Enseñanza Superior (DGESIC, Spain) through project PB94-0509, Universitat de Girona through project UdG98-452, Medichem S.A. (Barcelona) and Roviall Química S.L. (Murcia) is gratefully acknowledged. Thanks are also due to Dr. Llüisa Matas (Servei d'Análisi, Universitat de Girona) for recording the NMR spectra and performing the microanalyses. One of us (G.C.) wishes to thank the Ministerio de Educación y Ciencia (Spain) for a pre-doctoral fellowship.

References

1. Roxburg, C. J. *Synthesis* **1996**, 307.
2. Radesca, L.; Bowen, W. D.; Paolo, L. D.; Costa, B. R. d. *J. Med. Chem.* **1991**, *34*, 3058.
3. Rajagopalan, P.; Scribner, R. M.; Pennev, P.; Schmidt, W. K.; Tam, S. W.; Steinfels, G. F.; Cook, L. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 715.
4. Rajagopalan, P.; Scribner, R. M.; Pennev, P.; Mattei, P. L.; Kezar, H. S.; Cheng, C. Y.; Cheeseman, R. S.; Ganti, V. R.; Johnson, A. L.; Wuonola, M. A.; Schmidt, W. K.; Tam, S. W.; Steinfels, G. F.; Cook, L. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 721.
5. Cardillo, G.; Tomasini, C. *Chem. Rev.* **1996**, 117.
6. Jones, J. O.; McElhinney, R. S. *J. Chem Res. (S)* **1982**, 116.
7. Jones, J. O.; McElhinney, R. S. *J. Chem. Res. (S)* **1984**, 146.
8. Ghosh, A. K.; Thompson, W. J.; McKee, S. P.; Duong, T. T.; Lyle, T. A.; Chen, J. C.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 292.
9. Ghosh, A. K.; Thompson, W. J.; Lee, H. Y.; McKee, S. P.; Munson, P. M.; Duong, T. T.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 924.
10. Kim, B. M.; Lee, H.-Y.; Munson, P. M.; Guare, J. P.; McDonough, C. *Tetrahedron Lett.* **1993**, *34*, 6517.
11. Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.
12. Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis. Construction of Chiral Molecules using Amino Acids*; Wiley: New York, 1987.
13. Célimene, C.; Dihimane, H.; Bail, M. L.; Lhommet, G. *Tetrahedron Lett.* **1994**, *35*, 6105.
14. Bonin, M.; Grierson, D. S.; Royer, J.; Husson, H. P. *Org. Synth.* **1992**, *70*, 54.
15. Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83.
16. Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497.
17. Kobayashi, S.; Murakami, M.; Harada, T.; Mukaiyama, T. *Chem. Lett.* **1991**, 1341.
18. Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Tetrahedron Lett.* **1995**, *35*, 613.
19. Gallagher, D. J.; Wu, S.; Nikolic, N. A.; Beak, P. *J. Org. Chem.* **1995**, *60*, 8148.
20. Falorni, M.; Collu, C.; Giacomelli, G. *Tetrahedron: Asymmetry* **1996**, *7*, 2739.
21. Reiners, I.; Martens, J.; Schwarz, S.; Henkel, H. *Tetrahedron: Asymmetry* **1996**, *7*, 1763.
22. Segat-Dioury, F.; Lingibé, O.; Graffe, B.; Sacquet, M.-C.; Lhommet, G. *Tetrahedron* **2000**, *56*, 233.
23. Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 5517.
24. Andres, J. M.; Barrio, R.; Martinez, M. A.; Pedrosa, R.; Perez-Encabo, A. *J. Org. Chem.* **1996**, *61*, 4210.
25. Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 77.
26. Mordini, A.; Valacchi, M.; Pecchi, S.; Degl'Innocenti, A.; Reginato, G. *Tetrahedron Lett.* **1996**, *37*, 5209.
27. Obrecht, D. *Helv. Chim. Acta* **1989**, *72*, 447.
28. Masquelin, T.; Obrecht, D. *Tetrahedron Lett.* **1994**, *35*, 9387.
29. Masquelin, T.; Obrecht, D. *Synthesis* **1995**, 276.
30. Utimoto, K.; Miwa, H.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4277.
31. Masquelin, T.; Obrecht, D. *Tetrahedron* **1997**, *53*, 641.
32. Degl'Innocenti, A.; Scalfato, P.; Capperucci, A.; Bartoletti, L.; Mordini, A.; Reginato, G. *Tetrahedron Lett.* **1995**, *36*, 9031.

33. Garvey, D. S.; Wasicak, J. T.; Elliot, R. L.; Lebold, S. A.; Hettinger, A.-M.; Carrera, G. M.; Lin, N.-H.; He, Y.; Holladay, M. W.; Anderson, D. J.; Cadman, E. D.; Raszkiewicz, J. L.; Sullivan, J. P.; Arneric, S. P. *J. Med. Chem.* **1994**, *37*, 4455.
34. Falorni, M.; Giacomelli, G.; Spanedda, A. M. *Tetrahedron: Asymmetry* **1998**, *9*, 3039.
35. Chucholowski, A.; Masquelin, T.; Obrecht, D.; Stadlwieser, J.; Villalgordo, J. M. *Chimia* **1996**, *50*, 525.
36. Obrecht, D.; Abrecht, C.; Grieder, A.; Villalgordo, J. M. *Helv. Chim. Acta* **1997**, *80*, 65.
37. Serrat, X.; Cabarrocas, G.; Rafel, S.; Ventura, M.; Linden, A.; Villalgordo, J. M. *Tetrahedron: Asymmetry* **1999**, *10*, 3417.
38. Coispeau, G.; Elguero, J.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1970**, 689.
39. Xavier Serrat, PhD Thesis. University of Girona, 1999.
40. Johnson, C. K. ORTEP II, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.