Synthesis of Potentially β-Blocking Practolol Derivatives: (*E* + *Z*)-3-[4-(3-Iodoprop-2-enyloxycarbonylamino)phenoxy]-1-(isopropylamino)propan-2-ol

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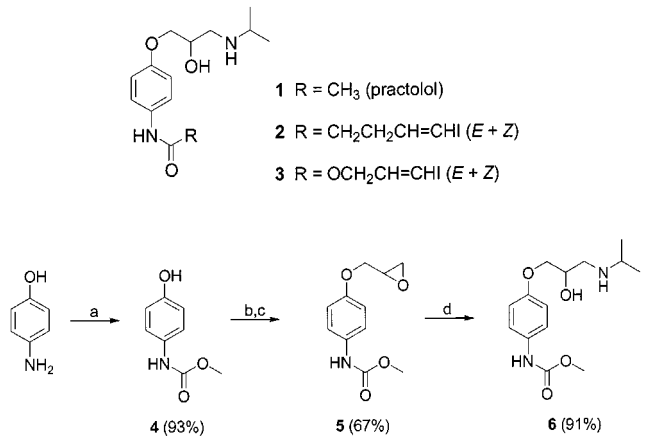
The iodinatied carbamates **3** (*E* + *Z*), with potential β-blocking properties, were synthesized. The first route chosen, from 4-aminophenol and the chloroformate **7**, had to be abandoned because of the formation of the oxazolidinone **10** during the epoxidation step. The aminoalcohol **17** prepared from the practolol **1** finally gave the target compounds by condensation with the iodoallylic chloroformates **8** (*E* + *Z*). The secondary Boc-protected amine function was regenerated without removing the carbamate function situated in the *p*-postion, by using mild reaction conditions (1 N HCl).

Introduction

During our studies on β-blockers, the iodinated analogues **2** (*E* + *Z*) of practolol **1** were synthesized.[1,2] The biological studies performed with this compound showed it to be of considerable interest.[3,4] Studies carried out by Kettmann et al. on a series of compounds structurally related to practolol, also revealed that the presence of the carbamate function in place of the amide function increased the blocking power by a factor of 10.[5] We therefore decided to synthesize the derivatives **3** (*E* + *Z*) in which R has the same number of links and the same iodinated terminal structure as **2** (*E* + *Z*), but with an oxygen instead of methylene bonded to nitrogen. Compound **6** (Scheme 1), an immediate derivative of practolol, was also prepared as a reference.

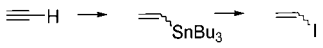


Scheme 1. a: $ClCO_2CH_3$, THF, CH_3CN, room temp.; b: NAH, DMF; c: glycidyl tosylate; d: $(CH_3)_2CHNH_2$, 2-propanol, reflux

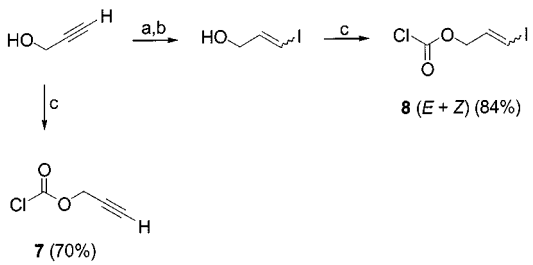
Results and Discussion

No particular problems were encountered with the synthesis of **6**, which had already been performed in a slightly different way.[5] However, a few remarks should be made concerning the epoxidation step. Contrary to what is normally observed, the phenol **4** did not disappear completely, even after a very long reaction time: 20% still remained after 24 h. Moreover, only the epoxide **5** was formed. From these results, it can be deduced that the NH group was probably more acidic than the OH group and that the amide ion formed was not nucleophilic.

It was first planned to use an identical route to obtain **3** (*E* + *Z*). In the first step, it was anticipated that the acetylenic chloroformate **7**, and not **8** (Scheme 2), would react with the aminophenol. In fact, while the initial biological studies can be carried out with the compound containing iodine-127, if the molecule proves to be of particular interest, further studies have to be carried out with the compound labeled with iodine-123. At the moment, the following sequence



is the best labeling method in the case of an iodovinylic structure, and far superior to I/*I isotopic exchange, which



Scheme 2. a: $HSnBu_3$, AlBN, toluene, reflux; b: ICI, CH_2Cl_2, room temp.; c: $ClCO_2CCl_3$, EtO_2, EtN_3, Ar, –30 °C

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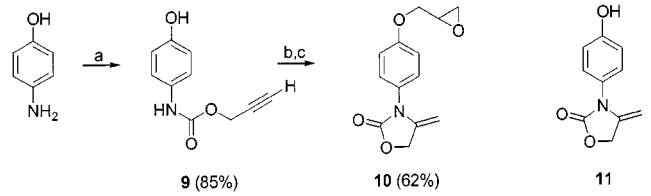
has produced only disappointing results.[6] Also, since iodine-123 has a very short half-life (13.2 h), $SnBu_3/I^*$ exchange must take place at the end of the synthesis. The synthesis route must therefore take into account these factors.

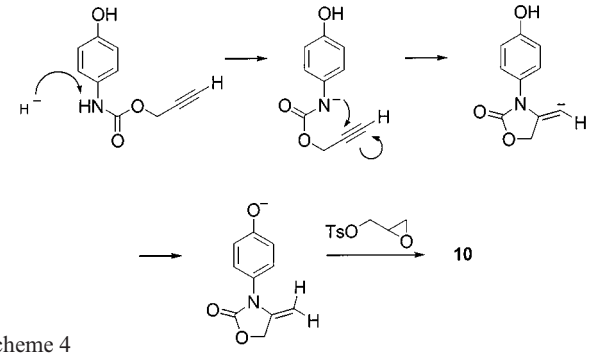
The derivative **7** was obtained relatively easily by operating at a low temperature, starting from propargyl alcohol and diphosgene in equimolar proportions. This excess of chlorinated reagent prevented the formation of the diacetylenic derivative.

While condensation of **7** with aminophenol led to the carbamate **9** with a very good yield, the subsequent step involving formation of the acetylenic epoxide led totally unexpectedly to **10** as the sole product (Scheme 3). Its structure was clearly identified on the basis of spectroscopic data.



Scheme 3. a: **7**, Et_3N, THF, CH_3CN, 5 °C, Ar; b: NaH, DMF; c: glycidyl tosylate

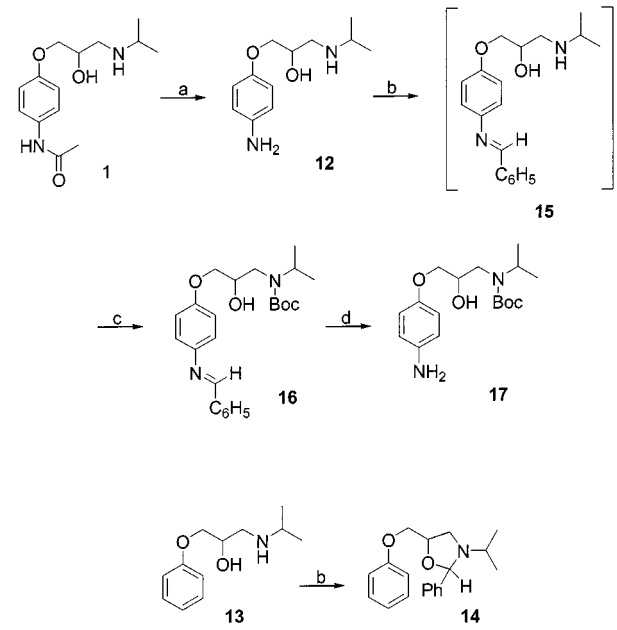
Proton NMR revealed, in addition to the signals characteristic of an epoxide ring and of a *p*-disubstituted aromatic structure, two multiplets situated between δ = 4.12–4.20 and δ = 5.0–5.04. These signals, each representing two protons, showed coupling only to themselves, as indicated by 2D analysis. ^{13}C NMR revealed the presence of three CH_2O and $=CH_2$. Finally, the molar mass was 247. The formation of **10** can, in fact, be explained quite easily in light of observations made during the preparation of **5**. When carbamate **9** was added to the hydride suspension, the hydrogen carried by the nitrogen should have been removed first to form an amide ion; because of the favourable entropic conditions, this led to ring formation. We were able to show that this ring formation occurred first. This was done by performing an hydrolysis, after completion of hydrogen evolution, and then analyzing the results. It was found that the starting compound had completely disappeared and only product **11** had formed. Moreover, the fact that the epoxide **10** was obtained after addition of the tosylate, shows that the phenolate was also formed. Scheme 4 shows the probable route through which these results were obtained. The amide ion formed initially reacted with the triple bond through



Scheme 4

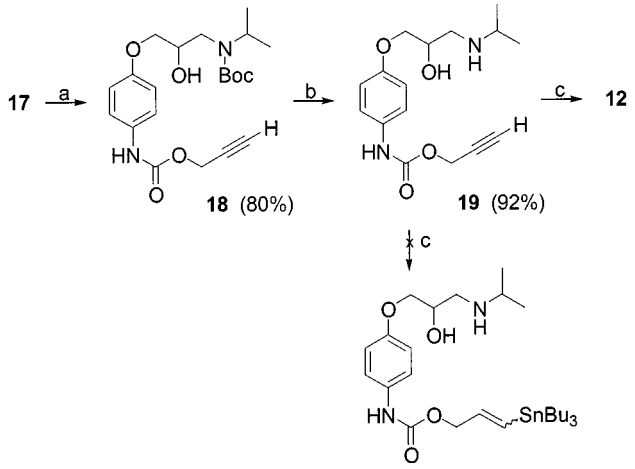
nucleophilic addition, which gave the most stable anion. This anion, which was very basic, removed the phenolic proton from another molecule. The phenolate thus obtained finally led to **10** after reaction with glycidyl tosylate.

Given that the desired results were not obtained by the synthesis route in which the carbamate function was introduced first, followed by the amino alcohol part, it was decided to reverse the order and first prepare compound **12** (Scheme 5). However, although the latter is obtained very easily from practolol [7–9] or 4-aminophenol, it has the disadvantage of having two amine functions. We therefore had to first find a way of protecting only the secondary amine function. Prugh et al. reported a simple but clever method for protecting a secondary amine function in the presence of a primary amine function.[10] It involves first preparing an imine through the action of benzaldehyde on the primary amine function, then protecting the secondary amine function with a *tert*-butoxycarbonyl (Boc) group and finally regenerating the primary amine function through hydrolysis of the imine using acid potassium sulfate. The three operations are performed in the same flask. But this method was developed for simple compounds with only the two amine functions. In the case of **12**, however, the presence of the hydroxyl group could lead to complications. In fact, there is a risk of formation of oxazolidines caused by the reaction of the amine and alcohol functions with the benzaldehyde.[11] Under Prugh's reaction conditions, compound **13** effectively leads almost quantitatively to the formation of **14** (*cis* + *trans*) (Scheme 5). However, with **12**, this ring formation did not occur and the desired compound **17** was obtained. Protection of the secondary amine function in this way may appear to complicate the synthesis, but it was in fact very simple to carry out. NMR was used to monitor the formation of **15**: the signal of the aldehydic proton at δ = 10 was replaced by that of the imine at δ = 8.5. Protec-



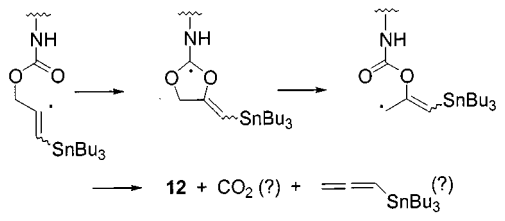
Scheme 5. a: 2 N HCl, reflux; b: C_6H_5CHO, benzene, reflux; c: $[(CH_3)_3COCO]_2O$; d: SiO_2

tion of the secondary amine function was then achieved at room temperature in the same flask. The next steps were then performed in a different way from that proposed by Prugh. In his case the hydrolysis was performed in the reaction medium, which means that the final mixture has to be completely treated: evaporation of the solvent followed by extraction with ether (to eliminate the neutral compounds), then addition of a base to free the primary amine. In our case, after elimination of the solvent, the residue (essentially **16**) was transferred directly to a chromatography (silica) column where both hydrolysis of the imine and separation of the different compounds were carried out. Finally, **17** was obtained with a minimum yield of 75% from **12**. The action of **7** gave compound **18** (Scheme 6) without any problems. This latter compound had the special characteristic of having two similar functions, since the secondary amine function was protected in the form of a carbamate. Reaction conditions therefore had to be found in which only the Boc group is removed. This group can be very easily eliminated using a 3 M hydrochloric acid solution in ethyl acetate.[12] Various tests in which the HCl concentrations were gradually reduced showed that only the carbamate carrying the *tert*-butyl was removed by a 1 N HCl solution in ethyl acetate. The derivative **19** was finally obtained with an excellent yield.



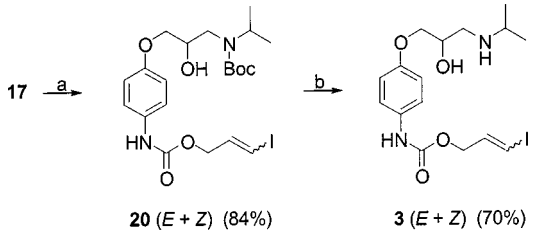
Scheme 6. a: **7**, Et_3N, THF, CH_3CN, 5 °C, Ar; b: N HCl, ethyl acetate; c: $HSnBu_3$, AlBN, toluene, reflux, Ar

The stannylation step which followed was unfortunately unsuccessful: only compound **12** was recovered. Scheme 7 illustrates an attempt to justify the formation of this product. The radical initially formed after the addition of $SnBu_3$ to the triple bond would be subject to 1,2-migration, leading to a cyclic radical.[13] Fragmentation of the latter would then afford the final products.



Scheme 7

The compounds **3** (*E* + *Z*) were finally prepared according to the route shown in Scheme 8. The iodinated allyl chloroformates **8** (*E* + *Z*) were obtained from propargyl alcohol[14] (Scheme 2). The stannylation conditions used gave a *E*/*Z* ratio of approximately 80/20. The action of the diphosgene on the iodoallyl alcohols gave the chloroformates with a good yield, provided low-temperature reaction conditions were used, and no attempt was made to purify (after treatment, the crude reaction mixture contained at least 90% of desired products). As in the case of **19**, following condensation between the amine **17** and **8** (*E* + *Z*), deprotection under mild conditions gave the compounds **3** (*E* + *Z*) with a good overall yield.



Scheme 8. a: **8**, Et_3N, THF, CH_3CN, Ar, 5 °C; b: N HCl, EtOAc

Conclusion

The carbamates **3** (*E* + *Z*) were synthesized in five steps from practolol. Iodine was introduced through condensation of the chloroformate of 3-iodoprop-2-enyl with the appropriate amino alcohol. Preliminary biological studies will determine whether these cold iodinated derivatives of practolol still have β−blocking properties and whether they should be labelled (with iodine-123) and studied more comprehensively. In this case, the synthesis route would have to be modified so as to be able to introduce the radioactive iodine (in electrophilic form) during the final step.

Experimental Section

General Methods: Reactions were monitored by TLC using alumina plates coated with silica gel $60F_{254}$ (Merck) and visualized using either UV light, iodine or by charring with phosphomolybdic acid (5% solution in ethanol). – Preparative chromatography was performed with Merck silica gel (0.063–0.200 mm). – Infrared spectra were recorded on thin films for the liquids and in nujol for the solids. – ^1H (^{13}C) NMR spectra were obtained on 200 (50 or 62.5) MHz spectrometers. Chemical shifts, for ^1H NMR spectra, are reported in δ units downfield from internal Me_4Si. ^{13}C NMR spectra were referenced to the $CDCl_3$ or [D_6]DMSO peak at δ = 77 or δ = 39.5, respectively, relative to Me_4Si. Multiplicities are reported as s (singlet), d (doublet), dd (doublet of doublet) t (triplet), m (multiplet). – Melting points were determined on a capillary melting

point apparatus and are uncorrected. – Elemental analyses were performed by the Central Analytical Service of the CNRS. DMF was distilled from (and stored over) 4Å molecular sieves. THF was distilled from sodium benzophenone ketyl immediately before use. Toluene and benzene were distilled from sodium. Acetonitrile was distilled from CaH_2. Organic layers were dried with anhydrous Na_2SO_4. Sodium hydride (60% in oil) was washed with pentane, under argon, three times before use.

4-(Methoxycarbonylamino)phenol (4): To a solution of 4-aminophenol (2 g, 18.35 mmol) in THF/acetonitrile (1:1, 40 mL) at room temp. under argon, was added dropwise methyl chloroformate (0.856 g, 9.06 mmol) in THF/acetonitrile (10 mL). The reaction was instantaneous. The hydrochloride was filtered and the solvents were evaporated. The residue was purified by column chromatography ($CHCl_3$/EtOAc = 3:2) to give **4** (1.41 g, 93%) as white crystals: m.p. 116 °C. – IR: $\tilde{\nu}$ = 3327, 1703 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$): δ = 3.74 (s, 3 H), 5.32 (s, H), 6.46 (s, H), 6.72–6.78 and 7.15–7.19 (2d, 4 H, *J* = 8.8 Hz). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 51.4, 115.1, 120.2, 130.6, 152.8, 154.2.

3-[4-(Methoxycarbonylamino)phenoxy]-1,2-epoxypropane (5): To a slurry of NaH (0.053 g, 1.32 mmol) in dry DMF (10 mL) at 0 °C was added dropwise under argon phenol **4** (0.200 g, 1.20 mmol) in DMF (10 mL). When the H_2 evolution stopped, glycidyl tosylate (0.274 g, 1.20 mmol) in DMF (5 mL) was added dropwise. After complete consumption of the phenol at room temp., the solvent was carefully removed and the resulting crude product dissolved in EtOAc. The solution was washed three times with water (3 × 15 mL), dried, concentrated in vacuo and the residue purified by column chromatography ($CHCl_3$/EtOAc = 4.5:0.5) to furnish **5** (0.180 g, 67%) as white crystals: m.p. 105–106 °C. – IR: $\tilde{\nu}$ = 3326, 1709 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$): δ = 2.73–2.77 (dd, H, *J* = 4.8 and 2.7 Hz), 2.88–2.93 (dd, H, *J* = 4.8 and 4.3 Hz), 3.31–3.38 (m, H), 3.76 (s, 3 H), 3.89–3.97 (dd, H, *J* = 11.0 Hz and 5.6 Hz), 4.17–4.24 (dd, H, *J* = 11.0 Hz and 3.2 Hz), 6.49 (s, H), 6.83–7.30 (m, 4 H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 44.7, 50.1, 52.3, 69.1, 115.0, 120.6, 131.4, 154.3, 154.8.

3-[4-(Methoxycarbonylamino)phenoxy]-1-isopropylaminopropan-2-ol 6: A solution of the preceding epoxide (0.140 g, 0.62 mmol) and isopropylamine (0.400 g, 6.76 mmol) in 2-propanol (25 mL) was heated at reflux for 2 h. After evaporation to dryness, the residue gave, after chromatography (EtOAc/MeOH = 3:2), product **6** (0.160 g, 91%) as a white solid; m.p. 116–117 °C. – IR: $\tilde{\nu}$ = 3314, 3284, 1715 cm^{-1}. – ^1H NMR (200 MHz, [D_6]DMSO): δ = 0.96–0.99 (d, 6 H, *J* = 6.2 Hz), 2.54–2.73 (m, 3 H), 3.32 (s, 2 H), 3.78–3.84 (m, 3 H), 6.83–7.34 (m, 4 H), 9.41 (s, H). – ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 22.7, 48.2, 49.9, 51.4, 68.2, 70.9, 114.6, 119.7, 132.1, 154.1, 154.2.

Prop-2-ynyl Chloroformate (7): Anhydrous ether (40 mL) was introduced under argon into a round-bottomed flask (500 mL) equipped with a thermometer, an argon inlet tube, a septum and a dropping funnel. After cooling to –10 °C in an acetone–dry ice bath, diphosgene (10 mL, 0.083 mol) was added with a syringe. The temperature of the cold bath was lowered to –20 °C and propargyl alcohol (4.64 g, 0.082 mol) in ether (100 mL) was added dropwise by means of the dropping funnel. Stirring was continued for 15 min at the same temperature. After cooling to –30 °C, triethylamine (11.5 mL, 0.083 mol) in ether (100 mL) was added dropwise (very slowly). Stirring was continued for a further 3 h, after which the mixture was allowed to warm to room temperature and stirred overnight. After bubbling with argon for 1 h, the reaction mixture was filtered. Evaporation of the solvent afford **7** (6.9 g, 70%) as an oil which was used in the next step without further purification. – IR: $\tilde{\nu}$ = 3308, 2141, 1789, 1141 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$): δ = 2.61–2.64 (t, H, *J* = 2.4 Hz), 4.82–4.83 (d, 2 H, *J* = 2.5 Hz). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 58.3, 75.0, 77.6, 150.4.

3-Iodoprop-2-enyl Chloroformate [(*E*+*Z*)-8]: The procedure was the same as for **7**. Diphosgene (0.66 mL, 5.47 mmol), 3-iodoprop-2-en-1-ol[14] (1 g, 5.43 mmol) and triethylamine (0.77 mL, 5.52 mmol) afforded, after filtration of the triethylammonium chloride precipitate and evaporation of the solvent (in vacuo, *without heating*), chloroformate **8** (*E* + *Z*) (1.13 g, 84%) as an oil, which was used in the next reaction without further purification. – IR: $\tilde{\nu}$ = 3061, 1777, 1610 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$): δ = 4.66–4.68 (m, 1.63 H, *E* isomer), 4.86–4.89 (dd, 0.37 H, *J* = 1.3 Hz and 5.9 Hz, *Z* isomer), 6.37–6.78 (m, 2 H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 72.1, 73.3, 84.8, 87.7 133.1, 136.9, 150.3. – $C_4H_4ClIO_2$: calcd. C 19.47, H 1.62, Cl 14.40, I 51.52; found (crude product) C 19.82, H 1.73, Cl 13.31, I 53.73.

4-(Prop-2-ynyloxycarbonylamino)phenol (9): To a solution of 4-aminophenol (1.10 g, 9.16 mmol) and triethylamine (1.42 mL, 10.08 mmol) in THF/acetonitrile (1:1, 30 mL) was added very slowly under argon at –35 °C a solution of compound **7** (1.09 g, 9.20 mmol) in THF/acetonitrile (1:1, 10 mL). The reaction mixture was kept at the same temperature during the addition, then allowed to warm to room temperature. After completion (TLC, $CHCl_3$/EtOAc = 4:1), the precipitate was filtered and the solvent evaporated in vacuo without heating. The residue was purified by chromatography to give **9** (1.49 g, 85%) as white crystals: m.p. 129–130 °C. – IR: $\tilde{\nu}$ = 3333, 3290, 2123, 1703 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$): δ = 2.49–2.50 (t, H, *J* = 2.4 Hz), 4.76–4.77 (d, 2 H, *J* = 2.4 Hz), 5.11 (s, H), 6.58 (s, H), 6.74–6.78 and 7.18–7.22 (2d, 4 H, *J* = 8.9 Hz). – ^{13}C NMR (62.5 MHz, [D_6]DMSO): δ = 51.7, 77.4, 79.2, 115.2, 120.2, 130.2, 152.8, 153.1. – $C_{10}H_9NO_3$: calcd. C 62.82, H 4.74, N 7.33; found C 63.18, H 4.62, N 7.03.

4-Methylene-*N*-[4-(2,3-epoxypropoxy)phenyl]-1-oxa-3-azolidin-2-one (10): Compound **10** was synthesized as described for **5** starting from **9** (0.200 g, 1.05 mmol), NaH (0.055 g, 1.24 mmol), glycidyl tosylate (0.240 g, 1.05 mmol). After flash chromatography ($CHCl_3$/EtOAc = 9:1) **10** was obtained as white crystals (0.160 g, 62%). – M.p. 95 °C. – IR: $\tilde{\nu}$ = 1771 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$) δ = 2.75–2.95 (m, 2 H), 3.35–3.37 (m, H), 3.91–4.00 (dd, H, *J* = 11.2 and 5.4 Hz), 4.12–4.20 (m, 2 H), 4.23–4.30 (dd, H, *J* = 11.2 and 2.6 Hz), 5.02–5.04 (m, 2 H), 6.99–7.04 and 7.23–7.27 (2d, 4 H, *J* = 8.4 Hz). – ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 44.0, 50.0, 67.1, 69.0, 81.8, 115.6, 126.5, 128.3, 142.1, 156.2, 158.2. – $C_{13}H_{13}NO_4$: calcd. C 63.15, H 5.26, N 5.67; found C 63.33, H 5.33, N 5.53.

4-Methylene-*N*-(4-hydroxyphenyl)-1-oxa-3-azolidin-2-one (11): A solution of **9** (0.200 g, 1.05 mmol) in anhydrous DMF (5 mL) was added dropwise at 0 °C under argon to a suspension of NaH (0.046 g, 1.15 mmol) in DMF (3 mL). When the evolution of H_2 stopped (2 h) the solution was hydrolyzed. TLC ($CHCl_3$/EtOAc/MeOH = 9:0.8:0.2) showed the presence of only one compound. The solvent was evaporated to dryness and the residue purified by chromatography to give **11** as yellowish crystals (0.13 g, 65%). M.p. 188–190 °C. – ^1H NMR (200 MHz, [D_6]DMSO): δ = 3.91–3.92 and 4.10–4.11 (m, 2 H), 5.07 (m, 2 H), 6.84–6.89 and 7.09–7.14 (2d, 4 H, *J* = 8.7 Hz), 9.78 (s, H). – ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 66.9, 80.7, 116.0, 124.5, 128.6, 143.1, 155.8, 157.3. – $C_{10}H_9NO_3$: calcd. C 62.82, H 4.71, N 7.33; found C 62.47, H 4.91, N 7.21.

3-[4-(Amino)phenoxy]-1-isopropylaminopropan-2-ol (12): A solution of practolol **1** (9.4 g, 35.3 mmol) in 2 N HCl (200 mL) was heated at reflux and the evolution of the reaction monitored by TLC (MeOH/28% NH_4OH = 100:4).[8] Upon completion of the reaction, the solution was made basic with $NaHCO_3$, to pH 8. After

evaporation to dryness, the residue (solid) was extracted with EtOAc (Soxhlet). The crude product (7.75 g) was purified by flash chromatography ($MeOH/NH_4OH$ = 100:1) to furnish **12** (7.23 g, 91%) as a white solid. Na_2O_2 could also be used to hydrolyze the amide.[9] A mixture of **1** (3 g, 11.3 mmol) and Na_2O_2 (1.76 g, 31.41 mmol) in water (110 mL) was heated at reflux and the reaction monitored by ^1H NMR (disappearance of the methyl singlet at δ = 2.14). After 3 h, the mixture was extracted with $CHCl_3$. The organic layer was worked up as usual to provide **12** (1.97 g, 78%) after column chromatography. This second way of hydrolysis is much easier to perform, but gives a lower yield: m.p. 115–118 °C. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.06–1.09 (d, 6 H, *J* = 6.2 Hz), 2.50–3.20 (m and br. s, 7 H), 3.86–4.05 (m, 3 H), 6.59–6.77 (2d, 4 H, *J* = 9.7 Hz). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.9, 48.8, 49.3, 68.5, 71.3, 115.6, 116.3, 140.1, 151.8.

3-[4-(Amino)phenoxy]-1-*N*-(*tert*-butoxycarbonyl)isopropylaminopropan-2-ol (17): A mixture of **12** (673 mg, 3.0 mmol), benzaldehyde (323 mg, 3.04 mmol) and benzene (35 mL) was heated at reflux and the water was removed, as it was formed, by means of a Dean–Stark apparatus. The reaction was monitored by NMR (disappearance of the signal at δ = 10 – aldehyde proton; appearance of a signal at δ = 8.5 – imine proton of **15**). After 3 h, the mixture was allowed to cool to room temp. and stirred for 24 h after the addition of di-*tert*-butyl dicarbonate (660 mg, 3.02 mmol). The liquid layer was evaporated in vacuo to provide 1.1 g (89%) of a very viscous residue, essentially **16** [$CHCl_3$/MeOH = 97.5:2.5; R_f = 0.42; visualization (phosphomolybdic acid): *grey spot of medium intensity*]. Column chromatography (silica gel: 80 g) of this product at slow flow rate (1 mL/5 min) afforded 690 mg of a very viscous product [$CHCl_3$/MeOH = 97.5:2.5; R_f = 0.25; visualization (phosphomolybdic acid): *very intense black spot*.]. Spectral analysis proved this product to be **17** (75% based on **12**). – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.14 (2 overlapping d, 6 H, *J* = 6.4 Hz), 1.47 (s, 9 H), 3.20–4.20 (m, 9 H), 6.61–6.75 (2d, 4 H, *J* = 9.0 Hz). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.4, 20.7, 28.3, 46.8, 48.6, 70.2, 71.7, 80.4, 115.4, 116.3, 140.1, 151.6, 156.3. – $C_{17}H_{28}N_2O_4$: calcd. C 62.96, H 8.64, N 8.64; found C 62.95, H 8.69, N 8.39.

5-Phenoxymethyl-2-phenyl-*N*-isopropyloxazolidine (14): This product was prepared, as described for **15**, from **13**[11] (0.80 g, 3.83 mmol), benzaldehyde (0.46 g, 4.34 mmol), benzene (60 mL), but not purified. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.99–1.07 (six signals, 6 H), 2.77–3.14 (m, 3 H), 3.93–4.17 (m, 2 H), 4.39–4.50 and 4.50–4.60 (2 m, H), 5.20 and 5.22 (2s, H), 6.86–6.98 (m, 3 H), 7.24–7.40 (m, 5 H), 7.48–7.55 (m, 2 H).

3-[4-(Prop-2-ynyloxycarbonylamino)phenoxy]-1-(*N*-*tert*-butoxycarbonyl)isopropylaminopropan-2-ol (18): Compound **18** was synthesized as described for **9** from **17** (0.780 g, 2.41 mmol), triethylamine (0.35 mL, 2.41 mmol) and **7** (0.284 g, 2.41 mmol) in THF/acetonitrile (1:1, 20 mL). After flash chromatography ($CHCl_3$/EtOAc = 9:1), **18** (0.783 g, 80%) was obtained as a very viscous oil. – IR: $\tilde{\nu}$ = 3290 cm^{-1}, 2252, 1727, 1672. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.12–1.19 (2 overlapping d, 6 H, *J* = 6.7 Hz), 1.48 (s, 9 H), 2.49–2.51 (t, H, *J* = 2.4 Hz), 3.20–3.50 (m, 3 H), 3.71–4.20 (m, 4 H), 4.76–4.77 (d, 2 H, *J* = 2.4 Hz), 6.64 (s, H), 6.84–6.88 and 7.26–7.31 (2d, 4 H, *J* = 9 Hz). – ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 20.5, 20.8, 48.7, 52.7, 69.9, 71.9, 74.9, 77.2, 80.6, 114.8, 120.6, 130.7, 152.7, 155.1. – $C_{21}H_{30}N_2O_6$: calcd. C 62.07, H 7.39, N 6.89; found C 62.55, H 7.23, N 6.92.

3-[4-(Prop-2-ynyloxycarbonylamino)phenoxy]-1-isopropylaminopropan-2-ol (19): Compound **18** (0.230 g, 0.57 mmol) was dissolved in a 1 M HCl solution in EtOAc (4 mL). The mixture was stirred at room temperature until the reaction was complete (3 h). The resulting chlorohydrate was extracted with water. The solution was made basic with $NaHCO_3$ and extracted with EtOAc. The combined extracts were dried and concentrated in vacuo. The residue was purified by chromatography (EtOAc/MeOH/27% NH_4OH = 4.2:0.8:0.1) to afford **19** (0.159 g, 92%) as a white powder: m.p. 96–97 °C. – IR: $\tilde{\nu}$ = 3438, 3314, 1746 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.36–1.40 (2 overlapping d, 6 H), 2.47–2.50 (t, H, *J* = 2.4 Hz), 3.00–3.40 (m, 3 H), 3.89–4.05 (m, 2 H), 4.35–4.52 (m, H), 4.74–4.75 (d, 2 H, *J* = 2.4 Hz), 5.25 (s, 2 H), 6.74–7.22 (m, 5 H). – ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 22.8, 22.9, 49.0, 49.1, 52.6, 68.2, 70.7, 74.9, 77.9, 114.9, 120.7, 130.7, 153.0, 155.2. – $C_{16}H_{22}N_2O_4$: calcd. C 62.74, H 7.19, N 9.15; found C 62.88, H 7.27, N 9.06.

3-[4-(3-Iodoprop-2-enyloxycarbonylamino)phenoxy]-1-*N*(*tert*-butoxycarbonyl)isopropylaminopropan-2-ol [(*E* + *Z*)-20]: The procedure was the same as for **9** starting from **17** (0.163 g, 0.50 mmol), triethylamine (0.07 mL, 0.55 mmol) and chloroformate **8** (0.123 g, 0.50 mmol) in anhydrous ether (15 mL). After flash chromatography ($CHCl_3$/EtOAc = 4:1), **20** (0.223 g, 84%) was obtained as a very viscous oil. – IR: $\tilde{\nu}$ = 3321, 1740, 1653 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.12–1.19 (2 overlapping d, 6 H, *J* = 6.6 Hz), 1.49 (s, 9 H), 3.37–3.39 (d, 2 H, *J* = 4.9 Hz), 3.75–4.80 (m, 4 H), 4.54–4.57 (dd, 1.26 H, *J* = 5.8 Hz and 0.9 Hz, *E* isomer), 4.72–4.91 (overlapping dd, 0.74 H, *Z* isomer), 4.91 (s, H), 6.49–6.76 (m, 3 H), 6.81–7.65 (m, 4 H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.5, 20.8, 28.4, 46.8, 48.6, 66.1, 67.3, 69.9, 71.7, 80.6, 80.9, 84.9, 114.8, 120.7, 130.9, 136.0, 139.9, 153.2, 154.9, 158.1. – $C_{20}H_{31}IN_2O_6$: calcd. C 45.97, H 5.93, I 24.33, N 5.36; found C 45.00, H 5.67, I 26.62, N 4.92.

3-[4-(3-Iodoprop-2-enyloxycarbonylamino)phenoxy]-1-isopropylaminopropan-2-ol [(*E* + *Z*)-3]: The procedure was the same as for **18**. Compound **20** (0.22 g, 0.41 mmol) gave, after column chromatography (EtOAc/CH_3OH/27% NH_4OH = 4:1:0.1), compound **3** (0.126 g, 70%) as yellowish crystals; m.p. 75 °C (decomp). – IR: $\tilde{\nu}$ = 3308, 1740 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.09–1.12 (d, 6 H, *J* = 6.3 Hz), 2.68–3.05 (m, 3 H), 3.39 (s, 2 H), 3.93–4.06 (m, 3 H), 4.27–4.74 (m, 2 H), 6.48–6.80 (m, 3 H), 6.83–7.26 (m, 4 H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.9, 49.0, 49.4, 66.3, 67.9, 70.7, 80.9, 84.8, 115.0, 120.8, 130.9, 136.0, 139.9, 153.2, 155.2. – $C_{16}H_{23}IN_2O_4$: calcd. C 44.24, H 5.30, I 29.26, N 6.45; found C 43.92, H 5.31, I 28.09, N 6.63.

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