Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 4895–4901

TETRAHEDRON: *ASYMMETRY*

Chiral azole derivatives. Part 5:† Synthesis of enantiomerically pure 1-[α-(benzofuran-2-yl)arylmethyl]-1*H*-1,2,4-triazoles, antifungal and antiaromatase agents

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Received 19 October 2000; accepted 5 December 2000

Abstract

Racemic and enantiopure benzofuranmethanamines **5a**–**c** have been reacted with *N*-Boc-3-(4-cyanophenyl)oxaziridine to give *N*-Boc-hydrazines **7a**–**c**, which have in turn been transformed by deprotection and cyclisation into triazoles **4a**–**c**, potent antiaromatase agents, in good overall yield and with high enantiomeric excess.

1. Introduction

Inhibition of the cytochrome P-450 enzyme aromatase has been recognized as a good therapeutic strategy for the treatment of estrogen-dependent breast cancers.[2] Efforts in this area have resulted in the identification of structurally diverse aromatase inhibitors, among which some 1-substituted azole (imidazole and 1,2,4-triazole) compounds proved to be potent, long-acting, and selective inhibitors. In particular, fadrozole hydrochloride **1**[3] and letrazole **2**[4] have been introduced into the clinical practice as antineoplastic drugs useful in the treatment of advanced, post-menopausal breast cancer and are devoid of significant side effects (Fig. 1).

Among aromatase inhibitors under investigation, 1-[2-benzofuranyl(4-chlorophenyl)methyl]-1*H*-imidazole (**3**, R = 4-Cl) has been shown to display potent activity both in vitro and in vivo,[5] with a 15-fold enantioselectivity (IC_{50} 5.3 nM versus 65.0 nM) in favor of the (+)-enantiomer,[6,7] whilst the racemic triazole derivative **4** (R = 4-Cl) proved to be an even more potent aromatase inhibitor.[7]

In connection with our investigations on chiral non-racemic azole compounds as antifungal and antiaromatase agents,[1,8] we have recently described the palladium-mediated heteroannulation of homochiral α-arylpropargylamines[9] to give enantiomerically pure or enriched α-aryl-2-

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0957-4166/00/$ - see front matter
PII: S0957-4166(00)00486-9

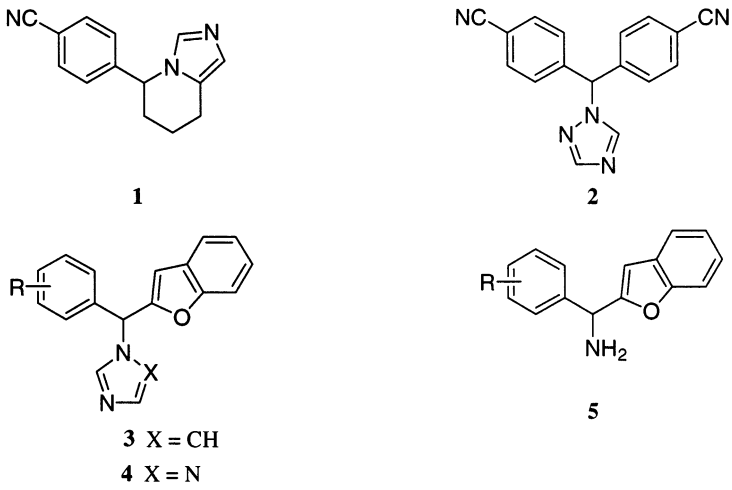
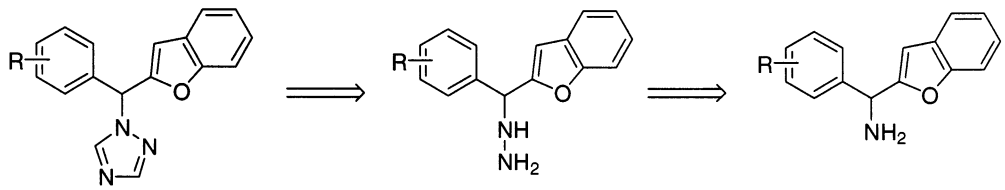


Figure 1.

benzofuranmethanamines **5**.[10] Pursuing the same research line, herein the first synthesis of homochiral 1-[α-(benzofuran-2-yl)arylmethyl]-1*H*-1,2,4-triazoles **4** is reported, according to the retrosynthetic approach depicted in Scheme 1.

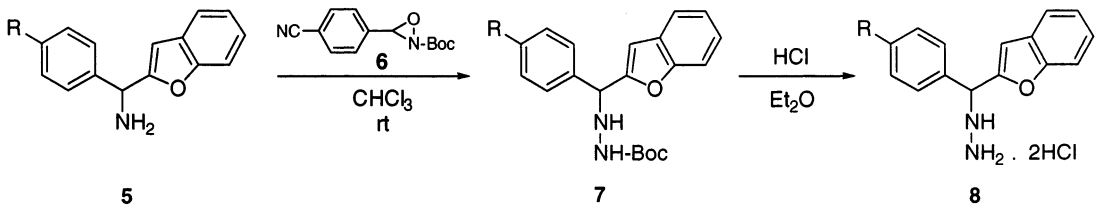


Scheme 1.

2. Results and discussion

Enantiomerically pure amines **5** were used as the starting materials for the synthesis of the target compounds **4**. First attempts to transform **5** into the corresponding hydrazino derivatives via nitrosation ($NaNO_2$, HCl, EtOH) followed by in situ reduction ($SnCl_2$, MeOH) of the intermediate *N*-nitroso compounds were unsuccessful, since only trace amounts of benzofuranmethanehydrazines could be detected by GC/MS. Therefore, we turned our attention to a new electrophilic aminating reagent recently developed by Vidal et al.,[11] namely *N*-Boc-3-(4-cyanophenyl)oxaziridine **6**.[12]

Reaction of benzofuranmethanamine (*R*)-**5a** (Scheme 2) with a stoichiometric amount of **6** in $CHCl_3$ at room temperature afforded the Boc-protected hydrazine (*R*)-**7a** in a 60% yield after chromatographic purification. Removal of the protecting group of **7a** with HCl/Et_2O gave the hydrazine dihydrochloride (*R*)-**8a** in 27% overall yield (Table 1) and with an enantiomeric excess $\geq 94\%$ (vide infra). Based on the assumption that the stereogenic center in the starting amine is not affected during this transformation, the absolute stereochemistry of (*R*)-**8a** can be assigned. Other enantiopure benzofuranmethanamines have been subjected to the same amination reac-



Scheme 2.

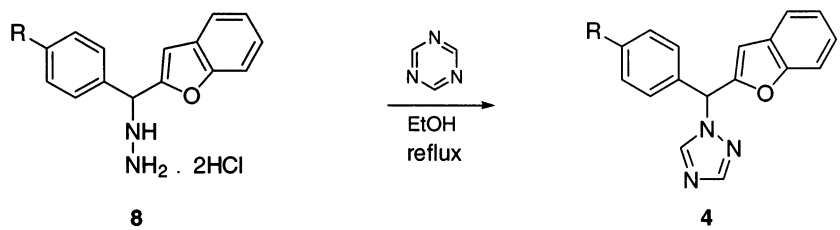
Table 1
Preparation of compounds **7** and **8**

Product	R	Time (h)	Yield (%)[a]	Mp (°C)
(*R*)-**7a**	H	22	66	Oil
(*R*)-**7b**	Cl	26	70	Oil
(*S*)-**7b**	Cl	26	68	Oil
(*R*)-**7c**	F	24	65	Oil
(*R*)-**8a**	H	2	50	190–191
(*R*)-**8b**	Cl	1.5	55	203–204
(*S*)-**8b**	Cl	1.5	55	202–203
(*R*)-**8c**	F	2	50	204–205

[a] Reaction yields refer to isolated and purified materials.

tion with **6**, followed by deprotection of the hydrazine group, to give compounds **8** in reasonable yield and with high enantiomeric excess.

Conversion of **8a–c** into the final triazoles **4a–c** was achieved using *s*-triazine as the cyclization reagent.[13] Thus, heating **8a–c** with *s*-triazine in refluxing EtOH (Scheme 3, Table 2) provided **4a–c** in 45–55% yield as yellowish oils.



Scheme 3.

Enantiomeric excesses were determined by enantioselective HPLC analyses (Fig. 2), while the absolute configurations were assigned based on those of the corresponding hydrazines. It should be pointed out that the enantiomeric excess of the resulting products **4** was always identical with that of the corresponding starting amines **5**, thus demonstrating the complete stereospecificity of the reaction sequence.

In conclusion, the first synthesis of triazoles of general structure **4** in homochiral form has been developed, thus allowing for the biological evaluation of single enantiomers of these pharmacologically relevant compounds. The results of the biological studies will be reported in due course.

Table 2
Synthesis of 1,2,4-triazoles **4**

Product	R	Time (h)	Yield (%)[a]	$[\alpha]_D^{23}$ [b]	Ee (%)[c]
(*R*)-**4a**[d]	H	8	50	+8.2 (*c* 0.23)	95
(*R*)-**4b**	Cl	10	55	+10.1 (*c* 0.97)	89
(*S*)-**4b**	Cl	10	55	−13.8 (*c* 1.83)	93
(*R*)-**4c**	F	11	52	+12.9 (*c* 0.16)	95

[a] Reaction yields refer to isolated and purified materials.
[b] Measured in chloroform solution.
[c] Enantiomeric excesses were determined by HPLC analyses on a Chiralcel OD column (Daicel Chemical Co., Ltd, 250 × 4.6 mm) eluting with *n*-hexane/isopropanol 90/10 (flow rate 1.0 ml/min).
[d] Absolute configurations were assigned based on those of the starting benzofuranmethanamines.

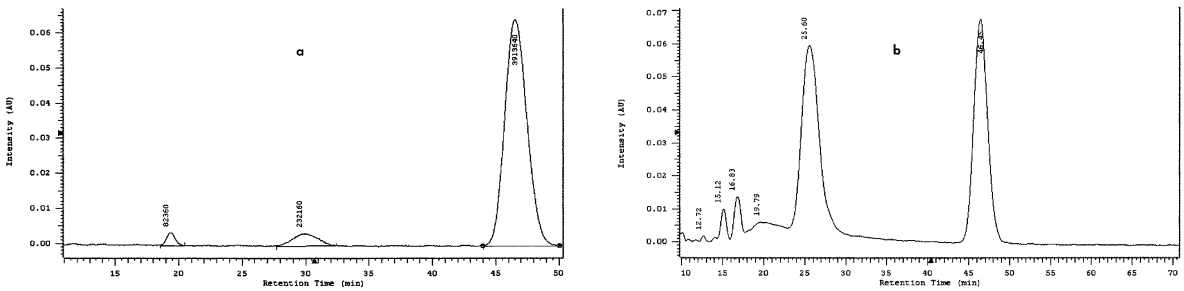


Figure 2. Chromatogram of (*S*)-**4b**: (a) in comparison with (*RS*)-**4a**, (b) (Chiralcel OD column, Daicel Chemical Co., Ltd, 250×4.6 mm, eluant*:* *n*-hexane/isopropanol 90/10, flow rate: 1.0 ml/min)

3. Experimental

3.1. General methods

Melting points were taken on a Gallenkamp apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. IR spectra were recorded on a Perkin–Elmer 1600 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were run on a Bruker AC 200 spectrometer at 200 MHz and 50 MHz, respectively. The chemical shifts are reported relative to $CDCl_3$ at δ 7.24 ppm and tetramethylsilane at δ 0.00 ppm. EI and FAB low-resolution mass spectra were recorded on a Saturn 2 spectrometer with an electron beam of 70 eV. Elemental analyses (C, H, N) were performed in house on a Perkin–Elmer 240C Analyzer. All reactions were carried out under an argon atmosphere. Organic solutions were dried over anhydrous sodium sulfate. Reagents were from commercial suppliers and used without further purification. *N*-Boc-3-(4-cyanophenyl)oxaziridine was prepared according to the reported procedure.[11]

3.2. Experimental methods

3.2.1. General procedure for the synthesis of Boc-protected hydrazines **7**

A solution of *N*-Boc-3-(4-cyanophenyl)oxaziridine **6** (1 mmol) in dry $CHCl_3$ (4 ml) was added dropwise to a solution of **5** (1 mmol) in dry $CHCl_3$ (4 ml) at 0°C. After stirring for 2 h at 0°C,

the solution was slowly warmed up to rt and then stirred for 20–24 h (Table 1) until the reaction was complete (TLC: silica gel, hexanes/ethyl acetate 4/3). Sodium borohydride (2 mmol) was added to reduce the by-product 4-cyanobenzaldehyde and make the purification step easier. Removal of the solvent under reduced pressure gave the crude product, which after purification by flash chromatography on silica gel (hexanes/$CHCl_3$/ethyl acetate = 10/7/1) afforded the pure product as a colorless oil. Selected data for these compounds are as follows.

3.2.1.1. (R)-*1-(*tert-*Butoxycarbonyl)-2-[α-(benzofuran-2-yl)phenylmethyl]hydrazine* ***7a***. IR ($CHCl_3$): 1706 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.44 (s, 9H), 4.70 (br s, 1H), 5.55 (s, 1H), 6.11 (br s, 1H), 6.62 (s, 1H), 7.16–7.58 (m, 9H). EIMS *m/z*: 338 [M^+], 281 [$M^+-C_4H_9$, 100%]. Anal. calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 71.29; H, 6.45; N, 8.05.

*3.2.1.2. (*R*)-1-(*tert-*Butoxycarbonyl)-2-[α-(benzofuran-2-yl)-(4-chlorophenyl)methyl]hydrazine* ***7b***. IR ($CHCl_3$): 1704 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.48 (s, 9H), 4.58 (br s, 1H), 5.47 (s, 1H), 6.28 (br s, 1H), 6.58 (s, 1H), 7.14–7.49 (s, 8H). EIMS *m/z*: 375/373 [M^++H]. Anal. calcd for $C_{20}H_{21}ClN_2O_3$: C, 64.43; H, 5.68; N, 7.51. Found: C, 64.64; H, 5.55; N, 7.30.

*3.2.1.3. (*S*)-1-(*tert-*Butoxycarbonyl)-2-[α-(benzofuran-2-yl)-(4-chlorophenyl)methyl]hydrazine* ***7b***. Same spectroscopic data as above. Anal. calcd for $C_{20}H_{21}ClN_2O_3$: C, 64.43; H, 5.68; N, 7.51. Found: C, 64.55; H, 5.60; N, 7.33.

*3.2.1.4. (*R*)-1-(*tert-*Butoxycarbonyl)-2-[α-(benzofuran-2-yl)-(4-fluorophenyl)methyl]hydrazine* ***7c***. IR ($CHCl_3$): 1704 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.44 (s, 9H), 4.60 (br s, 1H), 5.45 (s, 1H), 6.33 (br s, 1H), 6.97 (s, 1H), 6.98–7.22 (m, 4H), 7.44–7.63 (m, 4H). EIMS *m/z*: 355 [M^+–H], 225 [$M^+-C_4H_9OCONHNH$, 100%]. Anal. calcd for $C_{20}H_{21}FN_2O_3$: C, 67.40; H, 5.94; N, 7.86. Found: C, 67.62; H, 6.11; N, 7.60.

3.2.2. General procedure for the synthesis of hydrazine dihydrochlorides ***8***

Dry HCl gas was bubbled into a solution of **7** (1 mmol) in dry diethyl ether (15 ml) at 0°C for 30 min, then the reaction was stirred at rt for 1–1.5 h (Table 1). Removal of the solvent under reduced pressure left a yellowish solid, which was triturated with diethyl ether to give **8** as colorless crystals, which were recrystallized from ethanol/water. Selected data for these compounds are as follows.

*3.2.2.1. (*R*)-[α-(Benzofuran-2-yl)phenylmethyl]hydrazine dihydrochloride* ***8a***. ^1H NMR (CD_3OD): δ 5.31 (s, 1H), 6.45 (s, 1H), 7.14–7.60 (m, 9H). FABMS *m/z*: 239 [M^++H], 207 [$M^+-N_2H_3$, 100%]. Anal. calcd for $C_{15}H_{16}Cl_2N_2O$: C, 57.89; H, 5.18; N, 9.00. Found: C, 58.10; H, 5.23; N, 8.77.

*3.2.2.2. (*R*)-[α-(Benzofuran-2-yl)-(4-chlorophenyl)methyl]hydrazine dihydrochloride* ***8b***. ^1H NMR (CD_3OD): δ 5.72 (s, 1H), 6.67 (s, 1H), 7.32–7.49 (m, 8H). FABMS *m/z*: 275/273 [M^+–H]. Anal. calcd for $C_{15}H_{15}Cl_3N_2O$: C, 52.12; H, 4.37; N, 8.10. Found: C, 52.35; H, 4.43; N, 7.88.

*3.2.2.3. (*S*)-[α(Benzofuran-2-yl)-(4-chlorophenyl)methyl]hydrazine dihydrochloride* ***8b***. Same spectroscopic data as above. Anal. calcd for $C_{15}H_{15}Cl_3N_2O$: C, 52.12; H, 4.37; N, 8.10. Found: C, 51.92; H, 4.46; N, 7.90.

*3.2.2.4. (*R*)-[α-(Benzofuran-2-yl)-(4-fluorophenyl)methyl]hydrazine dihydrochloride* ***8c***. ^{1}H NMR (CD_3OD): δ 5.54 (s, 1H), 6.62 (s, 1H), 6.96–7.43 (m, 8H). FABMS m/z: 256 [M^+]. Anal. calcd for $C_{15}H_{15}Cl_2FN_2O$: C, 54.73; H, 4.59; N, 8.51. Found: C, 54.53; H, 4.68; N, 8.68.

3.2.3. General procedure for the synthesis of 1,2,4-triazoles ***4***

A solution of **8** (1 mmol) and *s*-triazine (6 mmol) in absolute EtOH (50 ml) was refluxed for 8–11 h (Table 2), then evaporated under reduced pressure. The residue was taken up into diethyl ether (50 ml) and this solution was washed with water (2×20 ml), brine (2×20 ml), then dried. Removal of the solvent left an oily residue, which was purified by flash chromatography on silica gel (hexanes/ethyl acetate = 1/1) to yield compounds **4** as light yellow oils. Selected data for these compounds are as follows.

*3.2.3.1. (*R*)-(+)-1-[α-(Benzofuran-2-yl)phenylmethyl]-1*H*-1,2,4-triazole* ***4a***. ^{1}H NMR ($CDCl_3$): δ 6.49 (s, 1H), 6.53 (s, 1H), 6.58 (s, 1H), 7.24–7.42 (m, 9H), 8.34 (s, 1H). EIMS m/z: 275 [M^+], 207 [$M^+-C_2H_2N_3$, 100%]. Anal. calcd for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found: C, 74.43; H, 4.88; N, 15.00.

*3.2.3.2. (*R*)-(+)-1-[α-(Benzofuran-2-yl)-(4-chlorophenyl)methyl]-1*H*-1,2,4-triazole* ***4b***. ^{1}H NMR ($CDCl_3$): δ 6.38 (s, 1H), 6.44 (s, 1H), 6.52 (s, 1H), 7.18–7.30 (m, 4H), 7.32–7.52 (m, 4H), 8.35 (s, 1H). EIMS m/z: 312/310 [M^++H]. Anal. calcd for $C_{17}H_{12}ClN_3O$: C, 65.92; H, 3.90; N, 13.57. Found: C, 66.19; H, 3.79; N, 13.84.

*3.2.3.3. (*S*)-(+)-1-[α-(Benzofuran-2yl)-(4-chlorophenyl)methyl]-1*H*-1,2,4-triazole* ***4c***. Same spectroscopic data as above. Anal. calcd for $C_{17}H_{12}ClN_3O$: C, 65.92; H, 3.90; N, 13.57. Found: C, 65.72; H, 3.76; N, 13.69.

*3.2.3.4. (*R*)-(+)-1-[α-(Benzofuran-2-yl)-(4-fluorophenyl)methyl]-1*H*-1,2,4-triazole* ***4c***. ^{1}H NMR ($CDCl_3$): δ 6.42 (s, 1H), 6.50 (s, 1H), 6.58 (s, 1H), 7.14–7.51 (m, 8H), 8.35 (s, 1H). EIMS m/z: 292 [M^+-H], 225 [$M^+-C_2H_2N_3$, 100%]. Anal. calcd for $C_{17}H_{12}FN_3O$: C, 69.62; H, 4.12; N, 14.33. Found: C, 69.48; H, 4.30; N, 14.45.

3.2.4. Enantioselective HPLC analysis

HPLC analysis was performed on Chiralcel OD column (4.6×250 mm), Daicel Chemical Co., Ltd, Japan. Mobile phase 10% isopropanol in hexane; flow rate 1 ml/min; $T = 25$°C; detection wavelength 250 nm. Retention times: (*S*)-**4a** 25.6; (*R*)-**4a** 46.5; (*S*)-**4b** 29.5; (*R*)-**4b** 46.6; (*S*)-**4c** 25.4; (*R*)-**4c** 41.7 min.

Acknowledgements

We thank Professor M. G. Quaglia Strano, University of Rome 'La Sapienza', for the determination of enantiomeric excess. This work was supported by the University of Siena (60% funds, 1999) and Italian CNR.

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