

Regio- and stereo-selective coupling reactions of heteroarylalkyl propargyl ethers with electrophiles

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Dedicated to Professor Mimmo Spinelli on his 70th birthday

(received 15 Oct 02; accepted 26 Dec 02; published on the web 03 Jan 03)

Abstract

Treatment of heteroarylalkyl propargyl ethers with *n*-BuLi affords relatively stable α - and α' -carbanions. Deprotonation performed in the presence of electrophiles leads to heteroaryl-substituted propargylic ethers and hydroxyalkylpropargylic ethers, containing new stereogenic centers. When the same reactions were carried out in the presence of an external chiral ligand, fairly good asymmetric induction was observed.

Keywords: Heterocycles, C–C coupling, heteroarylalkyl propargyl ethers, hydroxyalkyl propargylic ethers

Introduction

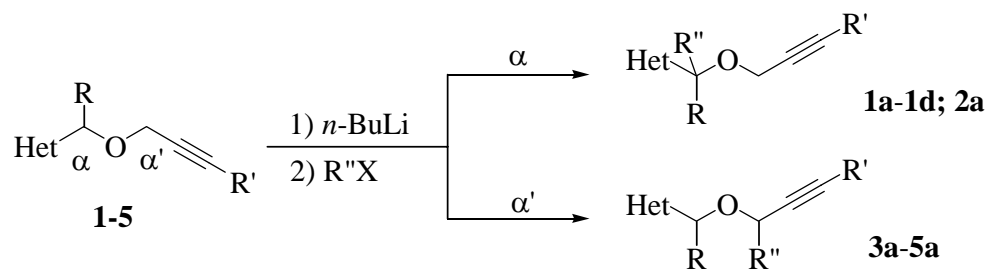
Carbanions α - to an aza- heterocycle are known to be relatively stable.¹ More interesting in synthetic organic chemistry are those carbanions which possess a further electron-withdrawing group. α -Chlorocarbenoids, prepared by deprotonation of the corresponding α -chloro-heteroaryl-alkanes, have been widely exploited as key intermediates in the synthesis of oxiranes² and aziridines.^{2c,3} Less studied as synthetic intermediates are those hetero-substituted carbenoids which possess in their framework an oxygen,^{4,5} a nitrogen, or a sulfur atom other than in the heterocycle.

We have recently shown that deprotonation (*n*-BuLi, THF at -78°C) of heteroarylalkyl propargyl ethers followed by acidic quenching leads to propargylic and allenic alcohols as a result of competitive [1,2]- and [2,3]-Wittig sigmatropic rearrangements.⁴ We have also reported that deprotonated allyl heteroarylalkyl ethers afford allylic and homoallylic alcohols.⁵ Such

rearrangements are likely to proceed by the same mechanisms,⁶ and specifically those reported by Nakai *et al.*^{6d,e,7} for analogous substrates, so that the [2,3]-Wittig rearrangement product would be the outcome of the α -carbon-atom deprotonation, while the [1,2]-Wittig rearrangement product would result from the deprotonation at the α' -carbon atom. The deprotonation occurred at the α - or at the α' -carbon atom depending on the acidifying effect of the substituents on the ether substrate. Our interest in the proposed mechanisms prompted us to investigate the behavior of heteroarylalkyl propargyl ethers when deprotonated in the presence of electrophiles. In this paper we report on the deprotonation of the aforementioned substrates with *n*-BuLi in THF at -78°C and the trapping of the resulting lithiated species with electrophiles. We report, also, the enantioselective coupling reactions of 2-(but-2-ynylloxymethyl)benzothiazole with a number of carbon electrophiles in the presence of a chiral ligand to afford hydroxy-substituted propargylic ethers. Hydroxypropargylic compounds of this kind have been prepared by electrochemical propargylation of aldehydes and ketones,⁸ or by α -chlorovinylolation of aldehydes, followed by a base-induced elimination.⁹ The coupling reaction of α -methoxybenzyl-lithium–chiral ligand complex with substituted propynals,¹⁰ or the addition of non-racemic propargylic mesylates to aldehydes¹¹ have been reported as providing enantioselective routes to hydroxypropargylic compounds.

Results and Discussion

The heteroarylalkyl propargyl ethers **1**–**5**, prepared as reported,⁴ were treated with *n*-BuLi in THF at -78°C , in the presence of various electrophiles (Scheme 1). The resulting lithiated species coupled efficiently with the electrophile; the outcome of the coupling reaction depending upon the heterocyclic group linked to the ether. The incoming electrophile goes to the α -carbon in the case of benzothiazolyl ethers, and to the α' -carbon atom with pyridyl-, thiazolyl-, and oxazolonyl ethers. Such a trend parallels the 1,2- and 2,3-Wittig rearrangements, which occur when the propargylic heteroaryl ethers are deprotonated in the absence of the external electrophile. Indeed, as anticipated in a previous paper, the deprotonation of 2-(but-2-ynylloxymethyl)benzothiazole **1** with *n*-BuLi in THF at -78°C , followed by the addition of iodomethane, afforded the 2-[1-(but-2-ynyl)oxy]ethyl]benzothiazole **1a**.⁴ Thus proving that the carbanion generation takes place at the α -carbon atom, immediately trapped by the CH_3I (Table 1: Entry 1).



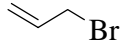
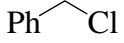
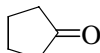
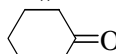
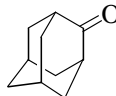
Substrate	Het	R	R'	R''X	Products
1		H	CH ₃	CH ₃ I	1a ^a
1	„	H	CH ₃	Si(CH ₃) ₃ Cl	1b
1	„	H	CH ₃		1c
1	„	H	CH ₃		1d
2	„	H	Ph	CH ₃ I	2a ^a
3		H	Ph	CH ₃ I	3a ^a
4		CH ₃	Ph	CH ₃ I	4a
5		CH ₃	Ph	CH ₃ I	5a

^a Compounds reported in a previous paper⁴ and listed in this Scheme only for comparison purposes.

Scheme 1. Coupling reactions of heteroarylalkyl propargyl ethers with alkyl halides.

Comparable results were obtained when the substrate **1** was deprotonated in the presence of different electrophiles, such as trimethylchlorosilane, allyl bromide, or benzyl chloride (entries 4, 5, and 6). The isolated reaction products were, again, coupling products at the α -carbon atom. Similarly, treatment of **2** with *n*-BuLi in the presence of CH₃I provided the α -carbon-atom-methylated compound **2a** as the sole reaction product (80% yield, entry 7). In contrast, treatment of 2-(3-phenylprop-2-ynoxy-methyl)pyridine **3** with *n*-BuLi in the presence of CH₃I afforded the methylation product **3a**, arising from the deprotonation at the α' -carbon atom (entry 8), together with the [1,2]-Wittig rearrangement product.⁴ Similarly, deprotonation–methylation of **4** produced the methylation product **4a**, arising again from the deprotonation at the α' -carbon atom (55% yield, entry 9), together with the [1,2]-Wittig rearrangement product. The deprotonation–methylation combination of 4,4-dimethyl-2-[1-(3-phenylprop-2-ynoxy)ethyl]-4,5-dihydro-1,3-oxazole **5** afforded compound **5a** (60% yield, entry 10) as the sole reaction product, arising from the deprotonation at the α' -carbon atom.

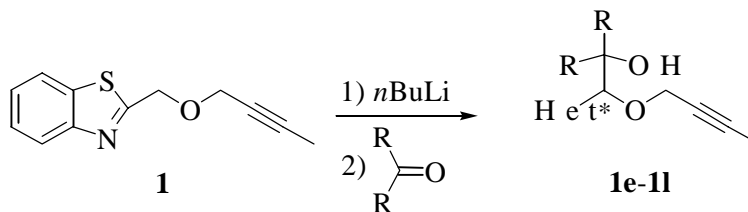
Table 1. Coupling reactions of heteroarylalkyl propargyl ethers with electrophiles

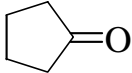
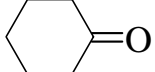
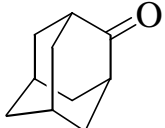
Entry	Substrate	Electrophile	Ligand	Solvent	Products (% yield) ^a	<i>ee</i> ^b	$[\alpha]_D^{22}$
1	1	CH ₃ I	–	THF	1a (95) ^c	–	–
2	1	„	(–)-sparteine	<i>n</i> -hexane	1a (40)	14	-12.5
3	1	„	„	toluene	1a (90)	60	-53.2
4	1	Si(CH ₃) ₃ Cl	–	THF	1b (78)	–	–
5	1		–	„	1c (60)	–	–
6	1		–	„	1d (50)	–	–
7	2	CH ₃ I	–	„	2a (80) ^c	–	–
8	3	„	–	„	3a (30) ^c	–	–
9	4	„	–	„	4a (55)	–	–
10	5	„	–	„	5a (60)	–	–
11	1	Me ₂ CO	–	„	1e (75)	–	–
12	1	„	(–)-sparteine	<i>n</i> -hexane	1e (40)	14	+15.3
13	1	„	„	toluene	1e (44)	64	+69.6
14	1	Et ₂ CO	–	THF	1f (70)	–	–
15	1	„	(–)-sparteine	<i>n</i> -hexane	1f (30)	20	+24.2
16	1	„	„	toluene	1f (60)	50	+60.9
17	1	<i>n</i> -Pr ₂ CO	–	THF	1g (79)	–	–
18	1	„	(–)-sparteine	<i>n</i> -hexane	1g (35)	16	+18.1
19	1	„	„	toluene	1g (57)	60	+65.4
20	1		–	THF	1h (81)	–	–
21	1	„	(–)-sparteine	<i>n</i> -hexane	1h (56)	50	+15.5
22	1	„	„	toluene	1h (59)	56	+17.3
23	1		–	THF	1i (90)	–	–
24	1		–	THF	1l (71)	–	–
25	1	„	(–)-sparteine	<i>n</i> -hexane	1l (70)	50	+11.1
26	1	„	„	toluene	1l (96)	60	+13.0

^a Isolated yields. ^b *ee* = enantiomeric enrichment. ^c Data reported in a previous paper ⁴ and listed in this Table only for comparison purposes.

The consideration that the deprotonation–alkylation sequence of the above propargylic ethers provides products with new stereogenic centres prompted us to investigate a possible asymmetric induction by using an external chiral ligand. The coupling reaction of the substrate **1** with iodomethane was then carried out in the presence of (–)-sparteine as the external chiral ligand, in

n-hexane and toluene (entries 2 and 3). A reasonable level of enantioselection was observed, and this seemed to be remarkably dependent upon the solvent used. In *n*-hexane, low enantioselectivity (*ee* = 14, entry 2) was observed; in toluene the methylated product **1a** was isolated with a good enantiomeric enrichment (*ee* = 60; entry 3), according to the results reported for asymmetric [2,3]-Wittig rearrangements of crotyl furfuryl ethers.¹² Encouraged by these findings, we performed several coupling reactions of substrate **1** with various symmetric ketones, obtaining hydroxypropargylic ethers as the only reaction products (Scheme 2).



1e	R, R =	CH ₃
1f	R, R =	CH ₂ CH ₃
1g	R, R =	CH ₂ CH ₂ CH ₃
1h	R, R =	
1i	R, R =	
1l	R, R =	

Scheme 2. Coupling reaction of 2-(but-2-ynyl)oxybenzothiazole, **1**, with symmetrical ketones.

In order to check the asymmetric induction in more detail, each reaction was performed in three different solvents: THF, *n*-hexane and toluene, in the presence of (–)-sparteine. The presence of the external chiral ligand usually lowered the yield of the coupling product. No enantioselection was observed in THF, and the lack of stereoselection could be ascribed to the THF's co-ordinating power, which probably prevents the generation of chiral co-ordinated intermediate involving the lithiated species and (–)-sparteine. In *n*-hexane, and especially in toluene, the (–)-sparteine allowed the formation of a chiral co-ordinated anion leading, by coupling with the corresponding ketone, to hydroxypropargylic ethers with remarkable enantiomeric enrichments (Table 1). The enantiomeric enrichments were measured, for almost all the reactions, by HPLC analyses (more details are given in the Experimental Section). The

enantiomeric enrichment of **1g** and **1i** (entries 18–19, 25–26) was measured by ^1H NMR analyses, calculating the integral's ratio of the two different broad signals given by the enantiomeric protons ($\delta = 5.30$ and 5.22 for **1g**, $\delta = 6.50$ and 5.60 for **1i**) distinguished by adding $\text{Eu}(\text{tfc})_3$ as chiral NMR shift reagent. When cyclohexanone was used as the electrophile (entry 23) neither HPLC, nor the ^1H NMR technique allowed us to measure any enantiomeric enrichment of **1i**.

In conclusion, we have shown that heteroarylalkyl propargyl ethers, deprotonated at the α -carbon atom or at the α' -carbon atom, depending on the stabilizing group of the carbanionic center, undergo a coupling reaction with a number of different electrophiles. Using this protocol, more complicated organic structures can be synthesized, such as compounds containing alkyl- or alcoholic functions. The carbanion complexation by an external chiral ligand leads to enantiomerically enriched mixtures ($ee = 64$). The option of freeing the acyl groups masked by the heterocycles (benzothiazole, thiazole, oxazoline) and the presence in their framework of various functions, makes them good intermediates for polyfunctional compounds such as heteroaryl hydroxy aldehydes which are of synthetic interest.

Experimental Section

General Procedures. *n*-BuLi was a commercial solution in hexanes (Aldrich) and was titrated with *N*-pivaloyl-*o*-toluidine prior to use.¹³ THF, *n*-hexane, toluene, (–)-sparteine, iodomethane, chlorotrimethylsilane, alkyl chlorides (allyl bromide, benzyl chloride), ketones (acetone, 3-pentanone, 4-heptanone, cyclopentanone, cyclohexanone, 2-adamantanone) were of commercial grade (Aldrich), as were europium D-3-trifluoroacetylcamphorate [$\text{Eu}(\text{tfc})_3$], and were used without further purification. Petroleum ether refers to the 40–60°C boiling fraction. The ^1H - and ^{13}C - NMR spectra were recorded with a Bruker AC 200 apparatus (200 MHz for ^1H , and 50.3 MHz for ^{13}C) with CDCl_3 as solvent and TMS as internal standard (chemical shifts in ppm: $\delta_{\text{H}} = 7.24$ for ^1H - spectra; $\delta_{\text{H}} = 77.0$ for ^{13}C - spectra). The IR spectra were recorded with a Perkin Elmer spectrometer Model 283. GC–MS analyses were performed with a Hewlett-Packard HP-5890 series II gas chromatograph (5% phenylmethylsiloxane capillary column, 30 m, 0.25 mm i.d.), equipped with an HP 5971 mass-selective detector operating at 70 eV (EI). A Jasco P-1020 polarimeter was used for polarimetric measurements. HPLC analyses were performed with a Hewlett-Packard system, 1100 series, containing a binary pump G1312A, a UV-variable-wavelength detector G1314A (detection at 254 nm) and equipped with a chiral column Chiracel OB–H. Eluent mixtures used for HPLC were *n*-hexane/ethanol or *n*-hexane/2-propanol. Melting points are uncorrected. TLC was performed on Merck silica gel plates with F-254 indicator; viewing was by UV light (254 nm). Column chromatography was performed on silica gel (63–200 μm), flash column chromatography was performed on silica gel (40–63 μm) with petroleum ether/diethyl ether (Et_2O) mixtures as eluents. All reactions involving air-sensitive

reagents were performed under nitrogen in oven-dried glassware using syringe/septum cap techniques.

General procedure for the coupling reactions of heteroarylalkyl propargyl ethers with alkyl halides

1a and **3a** were prepared as reported.⁴ The synthesis of the compound **1a** was performed also in the presence of (–)-sparteine (2 mmol) in *n*-hexane and toluene as solvent, following the same reported procedure.⁴ Compounds **1b**, **2a**, **4a**, and **5a** were prepared by stirring the corresponding pure product **1**, **2**, **4** or **5** (1 mmol) at –78°C in 15 mL of THF, adding dropwise, under N₂, first the corresponding alkyl halide (2 mmol) and then a solution of *n*-BuLi in hexanes (2.5 M, 0.5 mL, 1.25 mmol). After 30 min., the mixture was allowed to warm slowly to room temperature (over *ca.* 1 h), then quenched with 40 mL of a saturated aqueous NH₄Cl solution and extracted with Et₂O (3 x 20 mL). The combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo*. The crude products **1b** and **5a** were purified by flash column chromatography (silica gel: 40–63 μm; petroleum ether for **1b**, petroleum ether/Et₂O 1:1 for **5a**) to afford the pure heteroarylalkyl propargyl ethers (oils); yield, 78% and 60%, respectively. The crude products **2a** and **4a** were purified by column chromatography (silica gel: 63–200 μm; petroleum ether/Et₂O 1:1 for **2a** and 8:2 for **4a**) to afford the pure heteroarylalkyl propargyl ethers (**2a** solid, **4a** oil); yield, 80% and 55%, respectively. The compound **2a** can be synthesized alternatively by stirring a solution of 1-(benzothiazol-2-yl)ethanol and (3-chloroprop-2-ynyl)benzene in acetone/sodium hydroxide.⁴ Compounds **1c**, and **1d** were prepared by stirring the pure substrate **1** (1 mmol) at –78°C in 15 mL of THF, adding dropwise, under N₂, first a solution of *n*-BuLi in hexanes (2.5 M, 0.5 mL, 1.25 mmol) and then the corresponding alkyl halide (2 mmol). The mixtures were treated as reported above for the compound **1b**; the crude products were purified by column chromatography (silica gel 63–200 μm; petroleum ether/Et₂O, 1:1) to afford the pure heteroarylalkyl propargyl ethers **1c** and **1d**, (oils); yield, 60% and 50%, respectively.

2-[1-(But-2-ynyloxy)ethyl]benzothiazole (1a). In *n*-hexane; yield, 92 mg (40%), oil. HPLC: flow 0.3 ml/min., eluent, ethanol/*n*-hexane, 4:96, *ee* = 14. $[\alpha]_D^{22} = -12.5$. In toluene; yield, 208 mg (90%), oil. HPLC: flow 0.3 ml/min., eluent, ethanol/*n*-hexane, 4:96, *ee* = 60. $[\alpha]_D^{22} = -53.2$.

2-(But-2-ynyloxytrimethylsilanylmethyl)benzothiazole (1b). Yield, 225 mg (78%), oil. ¹H NMR (200 MHz, CDCl₃): δ = 0.13 (s, 9H), 1.85 (t, *J* = 2.3 Hz, 3H), 3.71–3.77 (m, 2H), 6.9 (s, 1H), 7.23–7.60 (m, 2H), 7.91 (dd, *J* = 1.3, 8.0 Hz, 1H), 8.05 (d, *J* = 7.7 Hz, 1H). ¹³C NMR (50.3 MHz, CDCl₃): δ = 1.8, 3.5, 59.2, 68.0, 73.9, 82.8, 121.7, 122.9, 125.0, 126.0, 134.9, 152.8, 175.0. GC-MS (EI, 70 eV) *m/z* (%): 289 (M⁺, 0), 216 (10), 202 (28), 149 (100). IR (CHCl₃): ν = 3060, 2920, 2860, 2220, 1520, 1440, 1350, 1100, 760, 730 cm⁻¹.

4-Methyl-2-[1-(1-methyl-3-phenylprop-2-ynyloxy)ethyl]thiazole (4a). Yield, 149 mg (55%), oil. ¹H NMR (200 MHz, CDCl₃): δ = 0.90 (d, *J* = 6.7 Hz, 3H), 1.65 (d, *J* = 6.7 Hz, 3H), 2.44 (s, 3H), 4.30 (q, *J* = 6.7 Hz, 1H), 5.0 (q, *J* = 6.7 Hz, 1H), 6.8 (s, 1H), 7.26–7.70 (m, 5H). ¹³C NMR (50.3 MHz, CDCl₃): δ = 16.3, 21.5, 22.8, 57.3, 74.0, 74.5, 83.0, 113.1, 128.0, 128.5, 131.5,

133.5, 152.4, 173.2 GC-MS (EI, 70 eV) m/z (%): 271 (M^+ , 6), 256 (20), 126 (90), 129 (100), 77 (25). IR (film): $\nu = 3055$ (br.), 2990, 2910, 2850, 2220, 1530, 1440, 1300, 1100 cm^{-1} .

4,4-Dimethyl-2-[1-(1-methyl-3-phenylprop-2-ynyloxy)ethyl]-4,5-dihydro-1,3-oxazole (5a). Yield, 163 mg (60%), oil. ^1H NMR (200 MHz, CDCl_3), $\delta = 1.30$ (d, $J = 6.6$ Hz, 3H), 1.34 (s, 6H), 1.45 (d, $J = 6.6$ Hz, 3H), 3.90 (s, 2H), 4.18 (q, $J = 6.6$ Hz, 1H), 4.45 (q, $J = 6.6$ Hz, 1H), 7.20–7.50 (m, 5H). ^{13}C NMR (50.3 MHz, CDCl_3), $\delta = 18.7, 21.0, 28.2, 57.1, 67.1, 69.9, 79.4, 84.8, 86.5, 122.5, 128.2, 128.4, 131.8, 165.0$. GC-MS (EI, 70 eV); m/z (%): 271 (M^+ , 1), 270 (1), 145 (45), 128 (53), 115 (24), 74 (100). IR (film): $\nu = 3060, 2980, 2850, 2225, 1660, 1100, 750, 690$ cm^{-1} .

2-(1-But-2-ynyloxybut-3-enyl)benzothiazole (1c). Yield, 154 mg (60%), oil. ^1H NMR (200 MHz, CDCl_3), $\delta = 1.83$ (t, $J = 2.0$ Hz, 3H), 2.76 (t, $J = 6.6$ Hz, 2H), 4.15 (dq, $J = 2.3, 15.0$ Hz, 1H), 4.28 (dq, $J = 2.3, 15.0$ Hz, 1H), 5.02–5.20 (m, 3H), 5.81–5.95 (m, 1H), 7.35–7.52 (m, 2H), 7.91 (d, $J = 7.7$ Hz, 1H), 8.00 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (50.3 MHz, CDCl_3): $\delta = 3.6, 40.8, 57.9, 77.2, 78.1, 83.4, 118.2, 121.8, 123.0, 125.1, 125.9, 132.8, 134.9, 153.7, 175.1$. GC-MS (EI, 70 eV); m/z (%), 257 (M^+ , 2), 242 (5), 216 (80), 204 (32), 189 (44), 164 (100). IR (film), $\nu = 3060, 2920, 2850, 2220, 1520, 1450, 1320, 1180, 1020, 920, 760, 730$ cm^{-1} .

2-(1-But-2-ynyloxy-2-phenylethyl)benzothiazole (1d). Yield, 153 mg (50%), oil. ^1H NMR (200 MHz, CDCl_3), $\delta = 1.56$ (t, $J = 2.5$ Hz, 3H), 3.89 (dq, $J = 2.5, 20.0$ Hz, 1H), 4.05 (dq, $J = 2.5, 20.0$ Hz, 1H), 5.08–5.27 (m, 2H), 6.50 (t, 6.8 Hz, 1H), 6.80–7.50 (m, 7H), 7.90 (dd, $J = 0.8, 7.5$ Hz, 1H), 7.99 (dd, $J = 0.8, 7.5$ Hz, 1H). ^{13}C NMR (50.3 MHz, CDCl_3), $\delta = 3.5, 39.2, 58.9, 69.7, 74.0, 85.2, 121.5, 122.1, 125.6, 126.8, 127.7, 128.2, 129.2, 130.0, 135.2, 152.1, 174.9$. GC-MS (EI, 70 eV); m/z (%), 307 (M^+ , 6), 254 (12), 216 (100), 164 (60), 91 (35). IR (film): $\nu = 3060, 3020, 2920, 2850, 2215, 1610, 1580, 1490, 1080, 1070, 750, 700$ cm^{-1} .

General procedure for the coupling reactions of 2-(but-2-ynyloxymethyl)benzothiazole 1 with symmetrical ketones

1e–1l were prepared by stirring the substrate **1** (1 mmol) in 15 mL of THF at -78°C [(–)-sparteine (2 mmol) was used with *n*-hexane or toluene as solvent], adding dropwise, under N_2 , first a solution of *n*-BuLi in hexanes (2.5 *M*, 0.5 mL, 1.25 mmol) and after 10 min. the corresponding ketone (2 mmol). After 30 min., the mixture was slowly allowed to warm to room temperature (over *ca.* 1 h), then quenched with 40 mL of a saturated aqueous NH_4Cl solution and extracted with Et_2O (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude products **1e–1l** were purified by column chromatography (silica gel 63–200 μm ; petroleum ether/ Et_2O , 1:1 for **1e**, 8:2 for **1f** and **1g**, 7:3 for **1h–1l**) to afford the pure heteroaryl hydroxypropargylic ethers (**1e–1i** oils, **1l** solid); yield, 70–90% in THF.

2-(Benzothiazol-2-yl-1-but-2-ynyloxymethyl)propan-2-ol (1e). In THF; yield, 206 mg (75%), oil. ^1H NMR (200 MHz, CDCl_3), $\delta = 1.29$ (s, 6H), 1.83 (t, $J = 2.3$ Hz, 3H), 2.90 (br. s, 1H, exchanges with D_2O), 4.20 (dq, $J = 2.3, 15.2$ Hz, 1H), 4.40 (dq, $J = 2.3, 15.2$ Hz, 1H), 4.80 (s, 1H), 7.35–7.54 (m, 2H), 7.90 (d, $J = 7.9$ Hz, 1H), 8.03 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (50.3 MHz,

CDCl_3), $\delta = 3.5, 25.5, 25.7, 59.0, 72.7, 74.1, 83.9, 84.3, 121.7, 123.0, 125.2, 126.1, 132.2, 153.0, 172.1$. GC-MS (EI, 70 eV); m/z (%), 275 (M^+ , 0), 217 (7), 164 (100), 136 (15), 109 (7). IR (film), $\nu = 3420$ (br.), 3060, 2970, 2910, 2850, 2220, 1500, 1440, 1370, 1310, 1160, 1070, 1020, 760, 730 cm^{-1} . In *n*-hexane; yield, 110 mg (40%), oil. HPLC; flow 0.5 ml/min.; eluent, 2-propanol/*n*-hexane, 5:95, *ee* = 14. $[\alpha]_{\text{D}}^{22} = +15.3$. In toluene; yield, 121 mg (44%), oil. HPLC: flow 0.5 ml/min., eluent, 2-propanol/*n*-hexane, 5:95, *ee* = 64. $[\alpha]_{\text{D}}^{22} = +69.6$.

3-(Benzothiazol-2-ylbut-2-ynyloxymethyl)pentan-3-ol (1f). In THF; yield, 212 mg (70%), oil. ^1H NMR (200 MHz, CDCl_3), $\delta = 0.92$ (t, $J = 7.0$ Hz, 3H), 0.95 (t, $J = 7.0$ Hz, 3H), 1.25–1.70 (m, 4H), 1.82 (t, $J = 2.3$ Hz, 3H), 2.40 (br. s, 1H, exchanges with D_2O), 4.08 (dq, $J = 2.3, 15.4$ Hz, 1H), 4.31 (dq, $J = 2.3, 15.4$ Hz, 1H), 4.94 (s, 1H), 7.35–7.50 (m, 2H), 7.90 (d, $J = 7.3$ Hz, 1H), 8.02 (d, $J = 7.5$ Hz, 1H). ^{13}C NMR (50.3 MHz, CDCl_3), $\delta = 3.6, 7.1, 7.8, 26.5, 27.6, 58.2, 74.3, 76.5, 81.3, 83.6, 121.7, 123.0, 125.2, 125.9, 135.3, 152.5, 171.3$. GC-MS (EI, 70 eV); m/z (%), 303 (M^+ , 0), 274 (2), 217 (8), 164 (100), 136 (9). IR (film); $\nu = 3430$ (br.), 3060, 2960, 2930, 2220, 1500, 1450, 1430, 1315, 1140, 1070, 1060, 760, 730 cm^{-1} . In *n*-hexane; yield, 91 mg (30%), oil. HPLC, flow 0.2 ml/min., eluent; ethanol/*n*-hexane, 1:99, *ee* = 20. $[\alpha]_{\text{D}}^{22} = +24.2$. In toluene; yield, 182 mg (60%), oil. HPLC: flow 0.2 ml/min., eluent, ethanol/*n*-hexane, 1:99, *ee* = 50. $[\alpha]_{\text{D}}^{22} = +60.9$.

4-(Benzothiazol-2-ylbut-2-ynyloxymethyl)heptan-4-ol (1g). Yield, 262 mg (79%), oil. ^1H NMR (200 MHz, CDCl_3), $\delta = 0.80$ – 0.95 (m, 6H), 1.36–1.80 (m, 8H), 1.81 (t, $J = 2.3$ Hz, 3H), 2.40 (br. s, 1H, exchanges with D_2O), 4.08 (dq, $J = 2.3, 15.4$ Hz, 1H), 4.31 (dq, $J = 2.3, 15.4$ Hz, 1H), 4.94 (s, 1H), 7.35–7.50 (m, 2H), 7.90 (d, $J = 7.3$ Hz, 1H), 8.02 (d, $J = 7.5$ Hz, 1H). ^{13}C NMR (50.3 MHz, CDCl_3), $\delta = 3.5, 14.5, 14.6, 16.2, 16.8, 36.8, 38.1, 58.2, 74.3, 76.2, 81.9, 83.5, 121.7, 123.0, 125.1, 125.8, 135.3, 152.5, 171.4$. GC-MS (EI, 70 eV); m/z (%), 331 (M^+ , 0), 217 (16), 164 (100), 149 (50), 136 (22). IR (film); $\nu = 3430$ (br.), 3060, 2970, 2860, 2225, 1500, 1450, 1430, 1315, 1140, 1070, 1000, 760, 730 cm^{-1} . In *n*-hexane; yield, 116 mg (35%), oil. ^1H NMR (200 MHz), adding $\text{Eu}(\text{tfc})_3$ $\delta = 5.30$ and 5.22 broad signals (enantiomeric protons), *ee* = 16. $[\alpha]_{\text{D}}^{22} = +18.1$. In toluene; yield, 189 mg (57%), oil. ^1H NMR (200 MHz), adding $\text{Eu}(\text{tfc})_3$ $\delta = 5.30$ and 5.22 broad signals (enantiomeric protons), *ee* = 60. $[\alpha]_{\text{D}}^{22} = +65.4$.

1-(Benzothiazol-2-ylbut-2-ynyloxymethyl)cyclopentanol (1h). Yield, 244 mg (81%), oil. ^1H NMR (200 MHz, CDCl_3), $\delta = 1.40$ – 1.90 (m, 8H), 1.82 (t, $J = 2.3$ Hz, 3H), 2.65 (br. s, 1H, exchanges with D_2O), 4.15 (dq, $J = 2.3, 12.0$ Hz, 1H), 4.34 (dq, $J = 2.3, 12.0$ Hz, 1H), 4.90 (s, 1H), 7.38–7.52 (m, 2H), 7.91 (d, $J = 7.4$ Hz, 1H), 8.03 (d, $J = 7.8$ Hz, 1H). ^{13}C NMR (50.3 MHz, CDCl_3), $\delta = 3.5, 24.0, 24.2, 36.0, 37.7, 58.5, 74.2, 82.8, 83.6, 83.7, 121.7, 123.1, 125.1, 125.9, 135.2, 152.7, 171.5$. GC-MS (EI, 70 eV); m/z (%), 301 (M^+ , 0), 248 (2), 217 (6), 164 (100), 136 (10), 109 (6). IR (film); $\nu = 3400$ (br.), 3060, 2960, 2920, 2850, 2220, 1500, 1430, 1315, 1080, 1020, 760, 730 cm^{-1} . In *n*-hexane, yield, 169 mg (56%), oil. HPLC; flow 0.3 ml/min., eluent, ethanol/*n*-hexane, 4:96, *ee* = 50. $[\alpha]_{\text{D}}^{22} = +15.5$. In toluene, yield, 178 mg (59%), oil. HPLC, flow 0.3 ml/min., eluent, ethanol/*n*-hexane, 4:96, *ee* = 56. $[\alpha]_{\text{D}}^{22} = +17.3$.

1-(Benzothiazol-2-ylbut-2-ynyloxymethyl)cyclohexanol (1i). Yield, 236 mg (90%), oil. ^1H NMR (200 MHz, CDCl_3), $\delta = 1.20$ – 1.70 (m, 10H), 1.80 (t, $J = 2.3$ Hz, 3H), 2.78 (br. s, 1H, exchanges with D_2O), 4.11 (dq, $J = 2.3, 15.4$ Hz, 1H), 4.35 (dq, $J = 2.3, 15.4$ Hz, 1H), 4.80 (s, 1H), 7.32–7.50 (m, 2H), 7.86 (d, $J = 7.9$ Hz, 1H), 7.99 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (50.3 MHz,

CDCl₃), δ = 3.6, 21.3, 21.5, 25.6, 33.3, 33.9, 58.6, 73.3, 74.2, 83.6, 83.8, 121.6, 123.0, 125.1, 125.8, 135.2, 153.2, 171.2. GC-MS (EI, 70 eV); m/z (%): 262 (M⁺, 0), 217 (10), 164 (100), 149 (3), 136 (8). IR (film); ν = 3420 (br.), 3060, 2930, 2850, 2230, 1500, 1440, 1315, 1080, 1050, 760, 730 cm⁻¹.

2-(Benzothiazol-2-ylbut-2-ynyloxymethyl)adamantan-2-ol (11). Yield, 261 mg (71%), m.p. 95–96°C (petroleum ether). ¹H NMR (200 MHz, CDCl₃), δ = 0.90–2.30 (m, 17H), 2.55 (br. s, 1H, exchanges with D₂O), 3.98 (dq, J = 2.2, 15.5 Hz, 1H), 4.21 (dq, J = 2.2, 15.5 Hz, 1H), 5.52 (s, 1H), 7.34–7.46 (m, 2H), 7.86 (d, J = 7.8 Hz, 1H), 8.01 (d, J = 8.1 Hz, 1H). ¹³C NMR (50.3 MHz, CDCl₃), δ = 3.6, 23.3, 24.3, 26.9, 27.2, 27.3, 32.9, 35.5, 36.9, 38.0, 74.7, 75.0, 76.5, 79.1, 83.2, 121.7, 123.1, 125.2, 125.7, 135.8, 152.1, 169.4. GC-MS (EI, 70 eV); m/z (%), 367 (M⁺, 1), 217 (11), 164 (100), 151 (6), 136 (6). IR (film), ν = 3400 (br.), 3060, 2910, 2850, 2225, 1600, 1450, 1350, 1315, 1140, 1060, 1010, 995, 760, 730 cm⁻¹. In *n*-hexane, yield, 257 mg (70%), solid. ¹H NMR (200 MHz, CDCl₃), adding Eu(tfc)₃ δ = 6.50 and 5.60 broad signals (enantiomeric protons), *ee* = 50. $[\alpha]_D^{22}$ = +11.1. In toluene, yield 352 mg (96%), solid. ¹H NMR (200 MHz, CDCl₃), adding Eu(tfc)₃ δ = 6.50 and 5.60 broad signals (enantiomeric protons), *ee* = 60. $[\alpha]_D^{22}$ = +13.0.

Acknowledgements

This work was carried out within the framework of the National Project “Stereoselezione in sintesi Organica: Metodologie ed Applicazioni” supported by the Ministero dell’Istruzione, dell’Università e della Ricerca, Rome. We also thank the Italian Consiglio Nazionale delle Ricerche (CNR), Rome and the University of Lecce for financial support.

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