Tetrahedron Letters 54 (2013) 5387–5390

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A stereoselective route to 6-substituted pyrrolo-1,5-benzoxazepinones and their analogues

Margherita Brindisi [a], Sandra Gemma [a], Gloria Alfano [a], Giridhar Kshirsagar [a], Ettore Novellino [b], Giuseppe Campiani [a,*], Stefania Butini [a]

[a] European Research Centre for Drug Discovery and Development (NatSynDrugs), University of Siena, via Aldo Moro 2, 53100 Siena, Italy
[b] Dipartimento di Farmacia, University of Naples Federico II, via D. Montesano 49, 80131 Naples, Italy

ARTICLE INFO

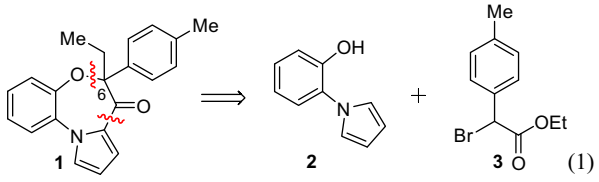
Article history:
Received 24 June 2013
Revised 17 July 2013
Accepted 22 July 2013
Available online 27 July 2013

Keywords:
Pyrrolo-1,5-benzoxazepinones
Aryl–alkyl ether
Menthol
Stereoselective synthesis

ABSTRACT

We developed a novel and convenient stereoselective path for the preparation of pyrrolo-1,5-benzoxazepinones (PBOs). This innovative route envisaged the employment of (−)-menthol as convenient chiral auxiliary and a key S_NAr for the stereoselective preparation of a tertiary aryl–alkyl ether. As a further advancement, we exploited this newly conceived synthetic route for the preparation of 2-substituted PBO analogues to either undergo biological evaluation themselves or give access to a variety of further functionalization options.

Pyrrolo-1,5-benzoxazepinones (PBOs) and pyrrolo-1,5-benzoxazepines (PBOXs) are pharmaceutically relevant heterocycles. In a variety of medicinal chemistry papers we highlighted the strong potential of these compounds as biologically active molecules, particularly as antitumor and antiviral agents.[1–7] As a part of our research activity, a major focus was directed toward the development of novel PBO compounds as nonnucleoside inhibitors of human immunodeficiency virus reverse transcriptase (HIV-1 RT)[1,2,4,6,7] and adenosine kinase (AK).[8] A number of extremely potent PBO antivirals were designed and synthesized and, in more recent papers, the stereoselective interaction with RT has been ascertained.[7] We recently discovered a new allosteric site for PBO on AK, making the survey of a stereoselective, versatile route to enantiomerically pure PBO compounds our priority in order to investigate the mode of interaction.[8] The traditional retrosynthetic approach for obtaining racemic PBOs envisaged the C6–O5 ether bond and the carbonyl group on the pyrrole ring as the key disconnection points, as shown for the representative compound **1** Eq. (1).[4] Alkylation of 2-(1*H*-pyrrol-1-yl)phenol **2** with the suitable α-bromophenylacetic esters **3**, followed by classical intramolecular Friedel–Crafts reaction and alkylation at C6, typically provided racemic PBOs in moderate to good overall yields.[4]



(1)

Although the enantiomers of PBO compounds proved to be separable by analytical HPLC,[7,8] the poor solubility of our racemates in typical mobile phases severely limits the scalability of this method. In addition, the oily nature of these compounds impeded their crystallization for X-ray analysis and for determining their absolute configuration. Therefore, we desired to develop an efficient, robust, and reproducible stereoselective strategy to generate PBO compounds. As illustrated in Figure 1 we reasoned that PBO scaffold (***R***)-**1** could be assembled from a chiral tertiary α-hydroxy acid (Synthon I) and an activated aryl fluoride (Synthon II).

The two synthons may be coupled together by means of a S_NAr reaction. The optically pure aryl–alkyl ether obtained would then undergo classical cyclization route. Furthermore, this newly conceived method could provide an easy access to 2-substituted PBO analogues (Fig. 1).

Chiral tertiary α-hydroxy acids are important building blocks[9–12] and synthetic intermediates[13–16] for the preparation of complex

* Corresponding author. Tel.: +39 0577 234172; fax: +39 0577 23234254.
E-mail address: campiani@unisi.it (G. Campiani).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.07.115

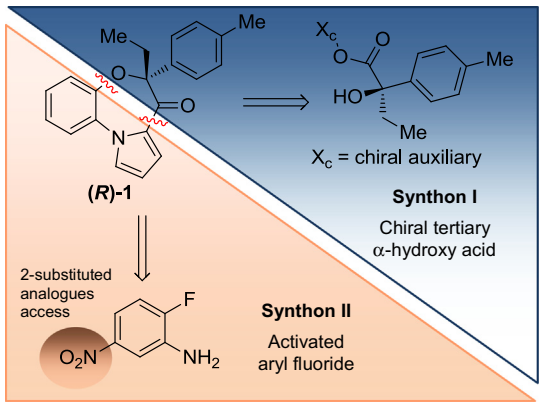


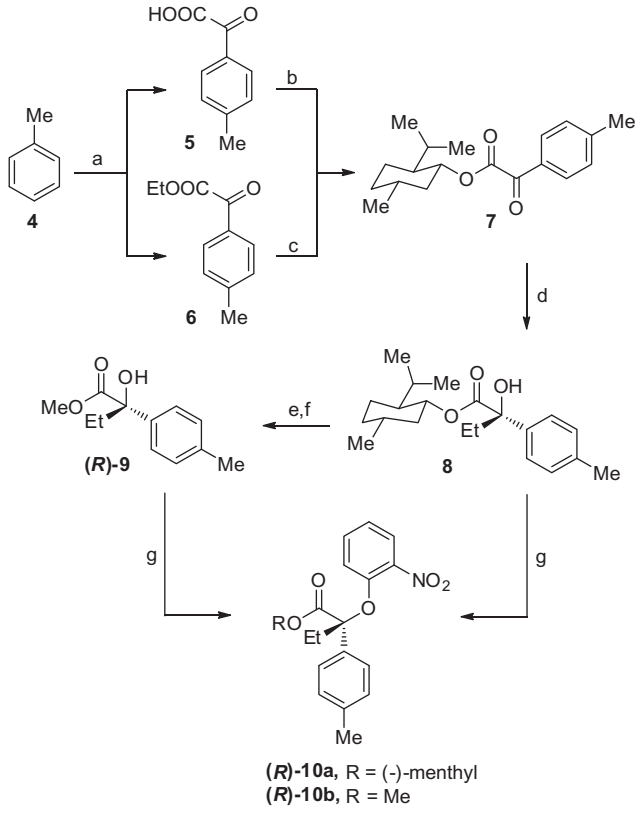
Figure 1. Proposed retrosynthetic approach for the stereoselective synthesis of PBO compounds and their 2-substituted analogues.

biologically active substances. The diastereoselective addition of organometallics to α-keto esters bearing cyclohexane-based chiral auxiliaries represents an efficient method for their stereoselective synthesis.[17–22] To this end, the use of menthol provides many advantages such as low cost, availability, and good selectivity.[16,23] Starting from toluene (**4,** Scheme 1), a standard Friedel–Crafts acylation protocol led to ethyl *p*-tolyl-oxo-acetate **6** and its corresponding free acid **5**, both employed for the preparation of the (−)-menthyl ester derivative **7**. Indeed, α-ketoacid **5** was condensed with (−)-menthol in the presence of *p*-toluenesulfonic acid,[22] while ester **6** underwent a modification of the titanium (IV) alkoxyde-catalyzed transesterification developed by Seebach.[24] Accordingly, treatment of **6** with (−)-menthol in the presence of a catalytic amount of titanium isopropoxide (20 mol %) in toluene at 100 °C provided the corresponding (−)-menthyl ester **7** in high yield (Scheme 1).

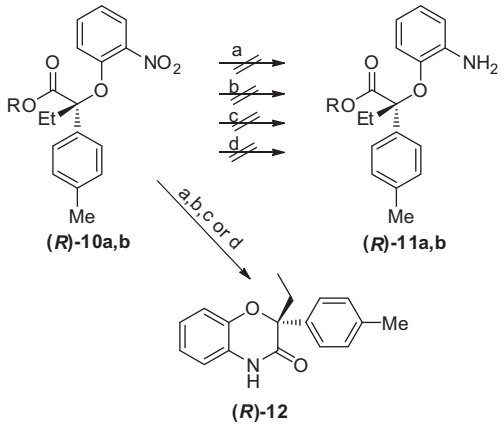
A number of literature examples show that ketones are suitable electrophiles to Grignard reagents. Furthermore, these experiments demonstrate how electrophilic addition of organometallics to α-menthyl keto esters provide better results in terms of selectivity when the Grignard reagent is used in the presence of zinc chloride.[17] In these systems in situ Mg/Zn transmetallation at the level of the Grignard reagent is accompanied by the parallel zinc chelation by the ketoester, thus favoring a *syn*-coplanar conformation for the two keto groups. Furthermore, an increased level of diastereoselectivity is reported if *para* position of an arylglyoxylate is occupied by an electrondonating group.[24] Accordingly, reaction of keto ester **7** with ethyl magnesium bromide in the presence of 2 equiv of zinc chloride afforded chiral α-hydroxy ester **8** (Scheme 1) in good yield and with a 92:8 dr by NMR determination (the two diastereoisomers being easily separated by flash chromatography). The ensuing conversion of menthyl ester to its corresponding methyl derivative was performed in order to overcome subsequent issues with the cleavage of menthyl ester on more hindered substrates which required harsh conditions and provided extremely poor yields. Saponification[22] provided the corresponding acid (analyzed by chiral HPLC to assess its optical purity)[25] in turn converted into the corresponding methyl ester (***R***)-**9** by a mild procedure employing methyl iodide in the presence of potassium carbonate (Scheme 1).[26]

As the next step we investigated nucleophilic aromatic substitution (S_NAr) by an alkoxide as a mild method to synthesize chiral tertiary aryl–alkyl ethers. Tertiary alkoxides are infrequently used as nucleophiles. Nevertheless, it has been observed that hindered tertiary alkoxides are effective nucleophiles in S_NAr reactions with activated aryl fluoride electrophiles.[27]

On these bases, we originally envisaged 1-fluoro-2-nitrobenzene as the suitable substrate for the S_NAr. The reaction, performed on both the (−)-menthyl ester **8** and the methyl ester (***R***)-**9** in the presence of sodium hydride as the base,[28] provided the desired ethers (***R***)-**10a,b** in good yields. No side-product indicative of radical nucleophilic substitution ($S_{RN}1$), such as hydro-de-halogenation products or biaryl products was observed. Furthermore, we



Scheme 1. Synthesis of aryl–alkyl ethers (***R***)-**10a,b**. Reagents and conditions: (a) $AlCl_3$, ClCOCOOEt, 1,2-DCE, 0 °C for 1 h then 30 °C for 4 h, 35% (for **5**) and 54% (for **6**); (b) (−)-menthol, *p*-TsOH, dry toluene, reflux, 20 h, 55%; (c) (−)-menthol, $Ti[OCH(CH_3)_2]_4$, dry toluene, 100 °C, 12 h, 67%; (d) EtMgBr (1 M solution in dry diethyl ether), $ZnCl_2$, dry diethyl ether, 0 °C for 2 h, −78 °C for 3 h, then 25 °C for 1 h, 85%; (e) KOH, MeOH/H_2O 1:1, reflux, 92%; (f) MeI, K_2CO_3, dry DMF, 25 °C, 4 h, 89%; (g) 1-fluoro-2-nitrobenzene, NaH, 15-crown-5, dry THF, 0 °C to rt, 17 h, 56% for (***R***)-**10a** and 62% for (***R***)-**10b**.



Scheme 2. Attempts to the synthesis of intermediates (***R***)-**11a,b**. Reagents and conditions: (a) H_2, Pd/C, EtOAc, rt, 30 min, 83%; (b) $HCOONH_4$, Pd/C, dry MeOH, rt, 12 h, 76%; (c) $SnCl_2{\cdot}2H_2O$, EtOAc, reflux, 2 h, 77%; (d) $NH_2NH_2{\cdot}H_2O$, Pd/C, EtOH, reflux, 3 h, 55%.

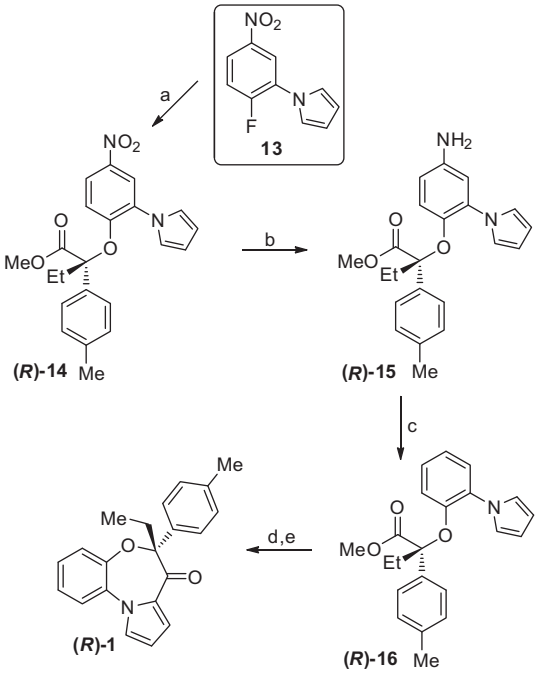
had no evidence of cine-substitution product, suggestive of benzyne-like intermediate formation. Regrettably, all the attempted reduction protocols on the nitro group of ethers (***R***)-**10a**,**b** (also employing aniline protecting agents, data not shown) for the following pyrrole ring construction led to the formation of the corresponding cyclic amide (***R***)-**12** (Scheme 2).

Although the benzoxazine nucleus was not useful for our purposes, the method described in Scheme 2 represents a straightforward and mild approach to optically pure benzoxazines substituted at C2, being the hydrogenolysis of the nitro group the most convenient method. Recently C2 substituted benzoxazines have been described as potent renin inhibitors.[28]

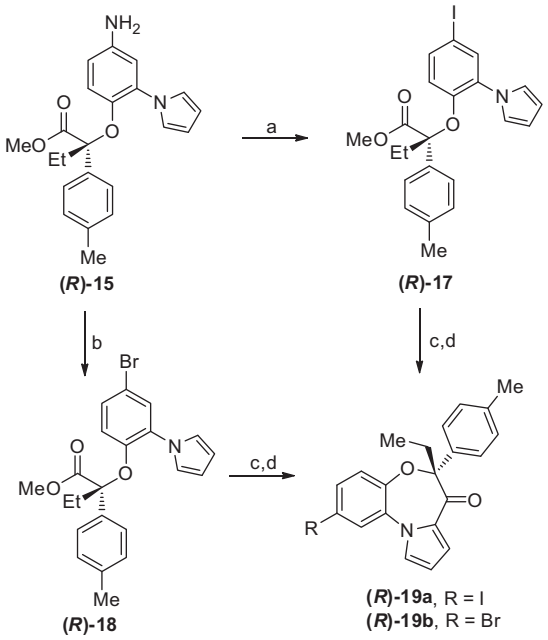
Taking a backward step, we reasoned that a S_NAr protocol could have also been applied on a different activated aryl fluoride, namely 4-nitro-2-pyrrolylfluorobenzene **13** (Scheme 3), deriving from its 2-amino derivative after a classical Clauson–Kaas pyrrole ring construction.[29] This substrate (**13**) would still represent a strongly activated fluoride, with the undeniable benefits of bearing at the same time the pyrrole ring already installed and the nitro group as useful entry for further functionalization. Notably, this approach allows avoiding the use of the Clauson–Kaas conditions on our aryl–alkyl ether. We also envisaged that the 'extra' nitro group could be suitably detached by a reductive deamination protocol.

Gratifyingly, S_NAr performed on derivative **13** provided the aryl–alkyl ether (***R***)-**14** in good yield, although lower than that obtained for compound (***R***)-**10b**, possibly due to the greater steric hindrance of the aryl fluoride **13**. Subsequent reduction performed with tin(II) chloride in refluxing ethanol led to aniline derivative (***R***)-**15**. The subsequent step was represented by a one-pot, diazotization–dediazotization to give the deaminated product (***R***)-**16** in moderate yield.

The reaction encompassed the use of sodium nitrite in the presence of acetic acid as a mild diazotization procedure and sodium bisulfite as the reducing agent.[30] Finally, starting from compound



Scheme 3. Stereoselective synthetic route of (***R***)-**1**. Reagents and conditions: (a) (***R***)-**9**, NaH, 15-crown-5, dry THF, 0 °C to rt, 17 h, 32%; (b) $SnCl_2{\cdot}2H_2O$, EtOH, reflux, 5 h, 90%; (c) $NaNO_2$, $NaHSO_3$, AcOH, EtOH, rt, 3 h, 31%; (d) 15% NaOH, THF/EtOH 1:1, reflux, 5 h, 99%; (e) PCl_5, dry CH_2Cl_2, 35 °C, 15 h, 20%.



Scheme 4. Synthesis of 2-bromo and 2-iodo derivatives (***R***)-**19a**,**b**. Reagents and conditions: (a) $NaNO_2$, KI, *p*-TsOH, H_2O, MeCN, 0 °C to rt, 2 h, 85%; (b) TMSBr, $NaNO_2$, TEBAC, CCl_4, 0 °C to rt, 36 h, 42%; (c) 15% NaOH, THF/EtOH 1:1, reflux, 5 h, 99%; (d) PCl_5, dry CH_2Cl_2, 35 °C, 15 h, 20–25%.

(***R***)-**16**, the synthetic route for the achievement of the PBO scaffold fully traced out the racemic synthesis, with alkaline hydrolysis of the methyl ester and subsequent intramolecular Friedel–Crafts reaction[4] leading to the desired (***R***)-**1** (Scheme 3).[31]

As a further advancement we intended to exploit this newly conceived synthetic route for the preparation of 2-substituted PBO derivatives to either undergo biological evaluation themselves or give access to a variety of functionalizations. Accordingly, aniline (***R***)-**15** was identified as a key versatile intermediate for this purpose. However, preliminary attempts of employing traditional Sandmeyer conditions led to complete decomposition of our starting material. As a consequence, we focused our attention on milder procedures providing halo-substituted analogues ((***R***)-**17** and (***R***)-**18**, Scheme 4). Iodination was indeed performed by using *p*-toluenesulfonic acid and sodium nitrite as mild diazotization agents in the presence of potassium iodide.[32] This protocol led to the iodo-derivative (***R***)-**17** in moderate yield. Aniline (***R***)-**15** was also converted into the corresponding bromo-derivative (***R***)-**18** in a one-pot reaction using sodium nitrite and bromotrimethylsilane in the presence of benzyltriethylammonium chloride (TEBAC) in carbon tetrachloride as the solvent. Bromotrimethylsilane was used for both the generation of the nitrosonium donor from sodium nitrite, and the substitution of the diazonium group.[33] Ester functionalities of (***R***)-**17** and (***R***)-**18** were hydrolyzed and the corresponding acids were submitted to intramolecular Friedel–Crafts cyclization providing the 2-substituted cyclic ketones (***R***)-**19a**,**b**.[4,34]

In conclusion, we herein developed a novel and convenient stereoselective path for the preparation of PBO compounds characterized by a quaternary chiral carbon atom at C6. This innovative route envisaged the employment of the naturally occurring menthol isomer as a convenient chiral auxiliary for the stereoselective preparation of the (*R*)-tertiary α-hydroxy acid and a key S_NAr reaction for the accomplishment of a stereochemically defined tertiary aryl–alkyl ether. As a further advancement we exploited this newly conceived synthetic route for the preparation of 2-substituted PBO analogues by the use of mild diazotization procedures which led to 2-bromo and 2-iodo PBO derivatives to either undergo biological

evaluation themselves or give access to a variety of further functionalizations (e.g., transition metal catalyzed reactions, alkoxylation). This method may be applied to the synthesis of enantiomerically pure pyrrolo-1,5-benzothiazepines calcium channel blockers, analogues of Diltiazem[35], and renin inhibitors based on a benzoxazine nucleus.[28]

Acknowledgment

Authors thank NatSynDrugs for financial support.

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