Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7285–7287

Expanding the medicinal chemistry toolbox: stereospecific generation of methyl group-containing propylene linkers

Kristopher Bosse, Jason Marineau, Deane M. Nason, Anton J. Fliri, Barb E. Segelstein, Kishor Desai and Robert A. Volkmann*

Pfizer Global Research and Development, Groton Laboratories, Pfizer Inc, Groton, CT 06340, United States

Received 11 February 2006; revised 9 August 2006; accepted 9 August 2006
Available online 30 August 2006

Abstract—Use of alkyl substituted propylene linkers as a strategy for fine-tuning the biological activity of medicinal agents requires ready access to these substrates. Herein, a general strategy is described for stereospecifically generating 18 chiral mono- and di-methylpropylene linkers. All twelve vicinal 1,2-propylene targets were generated from methyl-3-hydroxybutanoate and all 1,3-disubstituted targets from pentane-2,4-diol.

A number of strategies exist in medicinal chemistry for optimizing a molecule's biological profile. Rigid structural templates can favor the binding of ligands to proteins by ensuring the precise spatial orientation of important functional groups (pharmacophores). Flexible templates, however, also have an important role in disease intervention and rely on specific ligand conformations to achieve the same goal. In fact, many natural products and existing and potential drugs fall into this category. Favoring specific low-energy conformations of non-rigid molecules, however, is particularly challenging especially if key functional groups are separated by alkyl bridges bearing a number of rotating bonds. Because of the conformational flexibility of non-rigid molecules, strategies attempting to exploit specific ligand conformations are primarily guided by in silico predictors since closely related templates required to systematically investigate structure–function relationships are not available.

Herein, we provide a synthetic strategy for generating intermediates which provide an avenue for investigating the influence of acyclic conformational control on biological activity. The methodology provides propylene linkers containing methyl groups in all three positions of the chain. Substituted three carbon atom bridges were chosen for this investigation since they link amino and aryloxy moieties in a number of SSRI (selective serotonin reuptake inhibitors) antidepressants such as fluoxetine and *S*-duloxetine (Fig. 1). In addition, they have also been employed to couple basic groups such as piperazines and piperidines with aromatic moieties in a number of antipsychotic drugs (i.e., fluphenazine and domperidone, Fig. 1). Inserting methyl substituents on propylene linkers provides an attractive option for influencing the spatial orientation between groups at either end of the alkyl chain without dramatically affecting molecule size or lipophilicity.

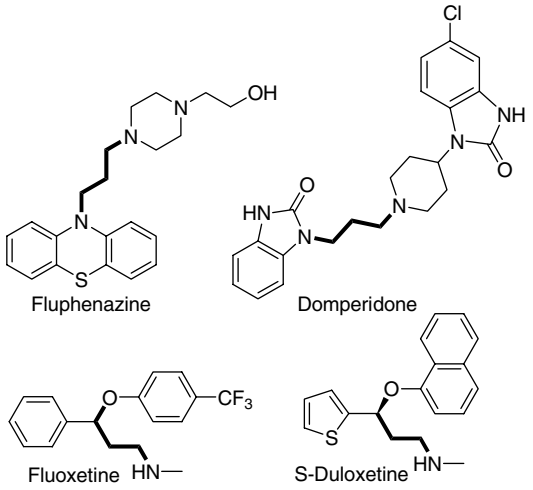


Figure 1. Medicines containing alkyl linkers.

* Corresponding author. Tel.: +1 860 441 4662; e-mail: robert.a.volkmann@pfizer.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.08.020

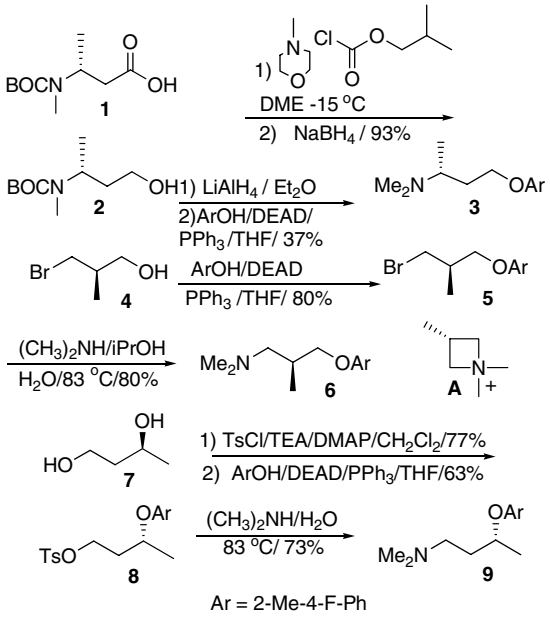
In total, 18 chiral aryloxyalkylamines (all the possible chiral propylene linkers containing one or two methyl groups) have been prepared. Having a general method for accessing the entire set of mono and 1,2- and 1,3-dimethyl propylene spacers within a series with documented biological activity (SRI) not only provides an opportunity for assessing the viability of the acyclic stereocontrol approach for fine-tuning biological activity in a series, but also provides valuable synthetic intermediates for accessing chiral 3-aminopropanols, 1,3-propanediols, and 1,3-propanediamines.

To ensure that the chemistry selected to access substituted propylene linkers would not only service our needs but would be broadly applicable to other related approaches, practical routes involving a minimal number of chiral starting materials were targeted. In the case of dimethyl substituted linkers, the intent was to exploit the reactivity difference between primary and secondary alcohols to control the regiospecificity of the reaction and obviate the need for protecting groups. Stereospecific Mitsunobu[1] and tosylate/mesylate displacements were chosen to incorporate phenoxy and amine substituents at secondary carbon atoms to ensure stereochemical integrity (inversion) at these centers.

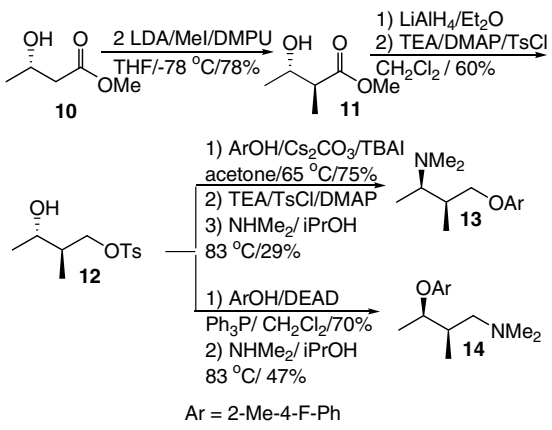
Stereospecific incorporation of a single methyl substituent in the propyl chain was easily achieved from commercially available starting materials (Scheme 1). Conversion of butanoic acid **1**[2] to alcohol **2** proceeded smoothly via sodium borohydride reduction of the mixed anhydride generated from **1**. Reduction of **2** with lithium aluminum hydride followed by Mitsunobu condensation of the primary alcohol with substituted phenols provided dimethylamine **3**.[3] Preparation of isomeric dimethylamine **6** was achieved in two steps from (*R*)-3-bromo-2-methylpropan-1-ol **4** following aryl ether formation to generate **5** and a subsequent dimethylamine-mediated bromine displacement. Interestingly, switching the sequence of the Mitsunobu and amination steps resulted in erosion of the optical purity of the product, implicating the intermediacy of the achiral 1,1,3-trimethylazetidinium intermediate **A**.[4] Accordingly, Mitsunobu condensation of (*S*)- and (*R*)-3-(dimethylamino)-2-methylpropan-1-ol with 3,4-dichlorophenol provided product ee's of 65–67%. The remaining monomethyl substituted aryloxyalkyldimethylamine **9** was prepared by selective monotosylation[5] of (*S*)-butane-1,3-diol **7** followed by a Mitsunobu-enabled secondary ether formation to provide tosylate **8**. Dimethylamine-mediated tosylate displacement cleanly provided **9**.

Propylene linkers containing vicinal dimethyl groups were accessed from readily available (*S*)-methyl-3-hydroxybutanoate **10**.[6] Alkylation of the dianion of **10** with methyl iodide using conditions described by Frater provided **11**.[7] Ester reduction with lithium aluminum hydride followed by selective alcohol tosylation (1.05 equiv tosyl chloride, −15 °C) afforded tosylate **12**.[5,8] Alcohol differentiation via selective tosylation allows for incorporation of amine and aryloxy substituents at either end of the propyl chain. Tosylate displacement by substituted phenoxides followed by tosylation of the secondary alcohol and amination with dimethylamine yielded **13**. Treatment of **12**, on the other hand, with phenols under Mitsunobu conditions to generate the corresponding aryl ether followed by tosylate displacement by dimethylamine afforded **14** (Scheme 2).

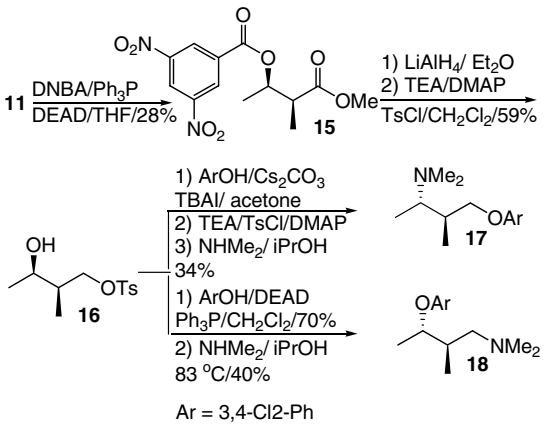
Inversion of the secondary alcohol center in **11** provides an opportunity to generate the remaining set of diastereomeric aryloxypropylamines. Treatment of (2*S*,3*S*)-methyl-3-hydroxy-2-methylbutanoate **11** with 3,5-dinitrobenzoic acid using standard Mitsunobu conditions[9] yielded 3,5-dinitrobenzoate **15**[10] (Scheme 3). Identical conditions utilized for the preparation of monotosylate **12** from **11** were utilized for converting **15** to **16**. In addition, conditions used for the syntheses of **13** and **14** were also utilized for the preparation of **17** and **18**.



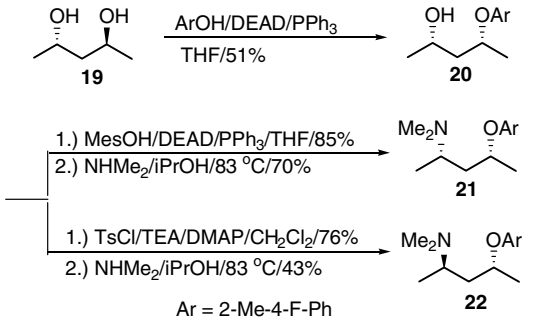
Scheme 1. Preparation of aryloxyalkylamines **3**, **6**, and **9**.



Scheme 2. Preparation of aryloxyalkylamines **13** and **14**.



Scheme 3. Preparation of aryloxypropylamines **17** and **18**.



Scheme 4. Preparation of 1,3-dimethylsubstituted **21** and **22**.

The final targets bearing methyl substituents at both ends of the propylene chain were generated from (2*S*,4*S*)-pentane-2,4-diol **19**. Mitsunobu condensations with substituted phenols provided (2*S*,4*R*)-4-phenoxypentan-2-ol **20**.[11] Having set the stereochemistry for the aryloxy substituent allows the preparation of both diastereomeric amines **21** and **22** from **20**. Treatment of **20** with methanesulfonic acid under Mitsunobu conditions[12] yielded intermediate mesylate (via inversion) which upon dimethylamine treatment provided **21**. Standard tosylation conditions (TsCl, TEA, DMAP, CH_2Cl_2) followed by dimethylamine treatment generated **22** (Scheme 4).

In summary, an efficient strategy has been developed for the synthesis of structurally related aryloxyalkylamines containing 18 chiral propylene linkers. While syntheses of the 2-methyl-4-fluoro- and 3,4-dichlorophenyl analogs are reported herein, the methodology has been employed to access other amine and phenyl analogs. In addition, intermediates described herein provide ready access to chiral 3-aminopropanols, 1,3-propanediols, and 1,3-propanediamines.

Acknowledgements

We are grateful to Jotham W. Coe and Professor Steven V. Ley for stimulating discussions.

Supplementary data

Synthetic procedures for the preparation of all intermediates and products. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.08.020.

References and notes

1. For examples of Mitsunobu reactions involving secondary centers, see: (a) Falkiewicz, B.; Kolodziejczyk, A. S.; Liberek, B.; Wisniewski, K. *Tetrahedron* **2001**, *57*, 7909–7917; (b) Castro, B. R. *Org. React.* **1983**, *29*, 1–162; (c) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127–164; (d) Shull, B. K.; Sakai, T.; Nichols, J. B.; Koreeda, M. *J. Org. Chem.* **1997**, *62*, 8294–8303.
2. (a) Hintermann, T.; Mathes, C.; Seebach, D. *Eur. J. Org. Chem.* **1998**, *11*, 2379–2387; (b) Matthews, J. L.; Overhand, M.; Kuhnle, F. N. M.; Ciceri, P. E.; Seebach, D. *Liebigs Annalen/Recueil* **1997**, *7*, 1371–1379.
3. Ibuki, T.; Sugihara, T.; Kawakubo, H.; Sone, T. U.S. 4,533,731; 1988.
4. Both enantiomers of **3** were generated and ratios were determined by chiral HPLC.
5. Najera, C.; Yus, M.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 289–300.
6. Asymmetric hydrogenation of methyl acetoacetate using (*S*)-BINAP–Ru as catalyst cleanly yields **10** (a) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856–5858; (b) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1991**, *32*, 4163–4166; (c) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Syn.* **1993**, *71*, 1; (d) Noyori, R. *Tetrahedron* **1994**, *50*, 4259–4292; Baker's yeast reduction provides an alternative source of **10** Kahn, M.; Fujita, K. *Tetrahedron* **1991**, *47*, 1137–1144.
7. Frater alkylation (a) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825–2829; (b) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2829–2832; (c) Frater, G.; Muller, U.; Gunther, W. *Tetrahedron* **1984**, *40*, 1269–1277; (d) Kraft, P.; Tochtermann, W. *Tetrahedron* **1995**, *51*, 10875–10882.
8. Pilli, R. A.; Bockelmann, M. A.; Del Corso, A. *J. Chem. Ecol.* **1999**, *25*, 355–368.
9. (a) Mitsunobu, O. *Synthesis* **1981**, *1*, 1–28; (b) Mori, K.; Watanabe, H. *Tetrahedron* **1985**, *41*, 3423–3428.
10. Gil, P.; Razkin, J.; Gonzalez, A. *Synthesis* **1998**, *4*, 386–392.
11. (a) Hagiya, K.; Yamasaki, A.; Okuyama, T.; Sugimura, T. *Tetrahedron: Asymmetry* **2004**, *15*, 1409–1417; (b) Brunner, H.; Obermann, U.; Wimmer, P. *Organometallics* **1989**, *8*, 821–826.
12. Davis, A. P.; Dresen, S.; Lawless, L. J. *Tetrahedron Lett.* **1997**, *38*, 4305–4308.