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Preparation of endothelin antagonist ABT-627

Steven J. Wittenberger * and Maureen A. McLaughlin

Abbott Laboratories, Pharmaceutical Products Division, Department of Process Research, 1401 Sheridan Road, D-45L, Bldg. R8, North Chicago, IL 60064-4000, USA

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Abstract

An enantioselective synthesis of ABT-627 is described. The key transformation is a diastereoselective 6-*endo-trig* cyclization to produce a 3,4,5-trisubstituted-1,2-oxazine which is ring contracted to the 2,3,4-tri-substituted-pyrrolidine core of ABT-627.

The endothelins (ET-1 and ET-3) are mitogenic 21-amino acid bicyclic peptides and are exquisitely potent vasoconstrictors.[1] Elevated ET levels have been noted in a variety of diseases including cerebral vasospasm, pulmonary hypertension, restenosis, and heart failure.[2,3] There are two endothelin receptors (ET_A and ET_B).[4] Selective blockade of the ET_A receptor subtype might provide therapeutic benefit in these and other disease states.[1] ABT-627 (**1**) is an extremely potent and selective endothelin receptor antagonist recently discovered at Abbott Laboratories.[5]

The initial synthesis of ABT-627 (**1**) was beset by poor diastereoselectivity and incorporated a late stage resolution to obtain optically pure material. The crux of our synthetic plan was to address the problems of relative and absolute stereocontrol that plagued the original synthesis of ABT-627.[5] We anticipated that arrangement of the substituents on a six-membered ring template rather than a five-membered ring would provide a better opportunity to control the relative stereochemistry. Retrosynthetically, the equatorially-substituted 1,2-oxazine **2** was envisioned to arise through a 6-*endo-trig* chair-like transition state **3** (Scheme 1). Addition of the ester enolate via its silyl ketene acetal to the trimethylsilyl triflate activated C=N double bond of the oxime ether would form the key carbon–carbon bond. The use of an oxygen atom as part of the six-membered ring served dual purposes. First, there already exist methods for the facile O-atom excision and ring contraction to the requisite five-membered ring structure. Second, the oxygen was a convenient point at which to bisect the molecule into readily prepared fragments. The cyclization precursor oxime ether **4** was to be constructed by the *O*-alkylation of the major *E*-aldoxime of *p*-anisaldehyde **5** with the optically active butyric ester derivative **6**. We chose to initially prepare this compound using Evans' asymmetric alkylation[6a] methodology following the closely related precedent of Schoenfelder et al.[6b]

* Corresponding author.

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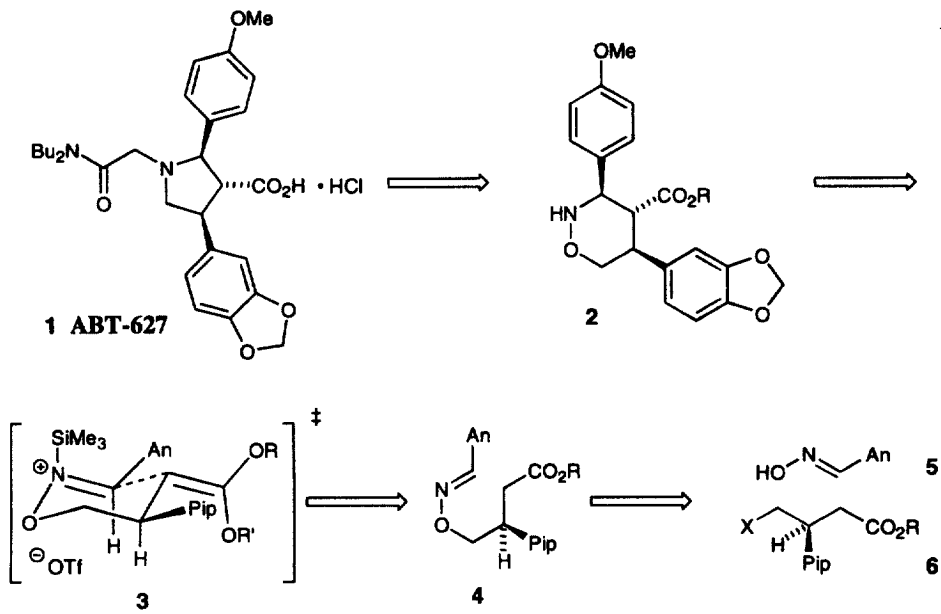
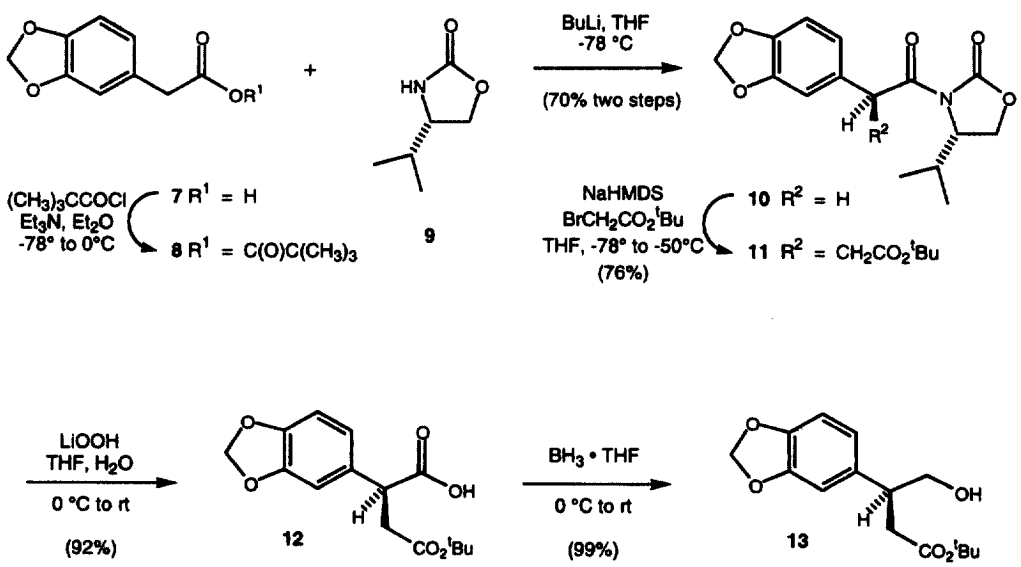


Scheme 1.

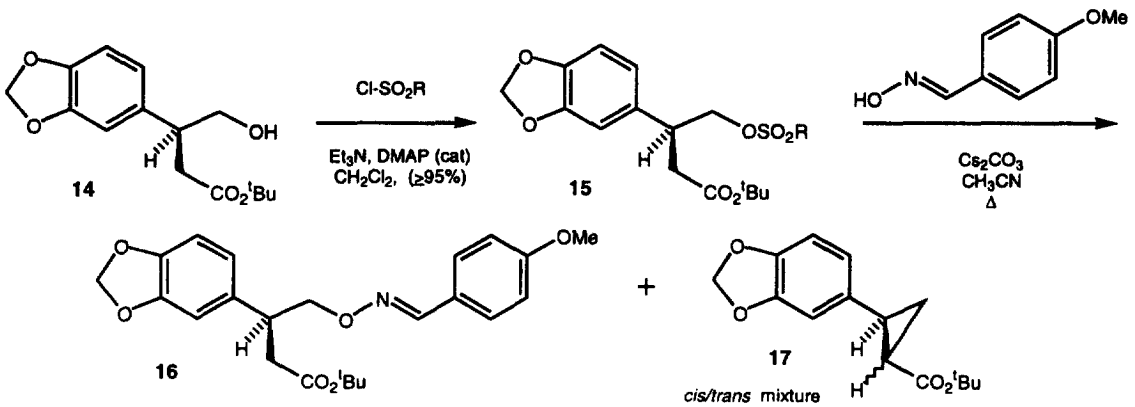
3,4-(Methylenedioxy)phenylacetic acid **7** was activated as the mixed anhydride **8** and treated with the lithium anion of the valine derived oxazolidinone **9** to give the acyl oxazolidinone **10** in 70% yield (Scheme 2). Treatment of the sodium anion of **10** with *t*-butyl bromoacetate gave **11** in 76% yield. Hydrolysis of chiral auxiliary was effected by lithium hydroperoxide[7] and the resulting carboxylic acid **12** (93% ee by chiral HPLC assay) was reduced with borane–THF complex to give the alcohol **13**.



Scheme 2.

We investigated the *O*-alkylation of *p*-anisaldehyde oxime **5** (*E*:*Z*=8:1) with a series of sulfonate esters **15** prepared from alcohol **13** by standard methods (Scheme 3). In general, the alkylation reaction was faster and cleaner with cesium carbonate than with potassium, sodium carbonate or amine bases, and acetonitrile was the best of the polar aprotic solvents tested. In addition to the desired *E*-oxime

ether **16**, the separable *Z*-oxime ether isomer of **16** (structure not shown, ratio~8:1 *E*:*Z*) and variable amounts of cyclopropane **17** (*cis/trans* mixture) were observed as side products. Aryl sulfonates were preferred to the mesylate. The optimized reaction conditions entail use of the 4-chlorophenyl sulfonate (**15**, R=4-ClC$_6$H$_4$-) to yield *E*-oxime ether **16** in 79% yield, *Z*-oxime ether in ~10% yield, and <5–7% cyclopropane **17**.

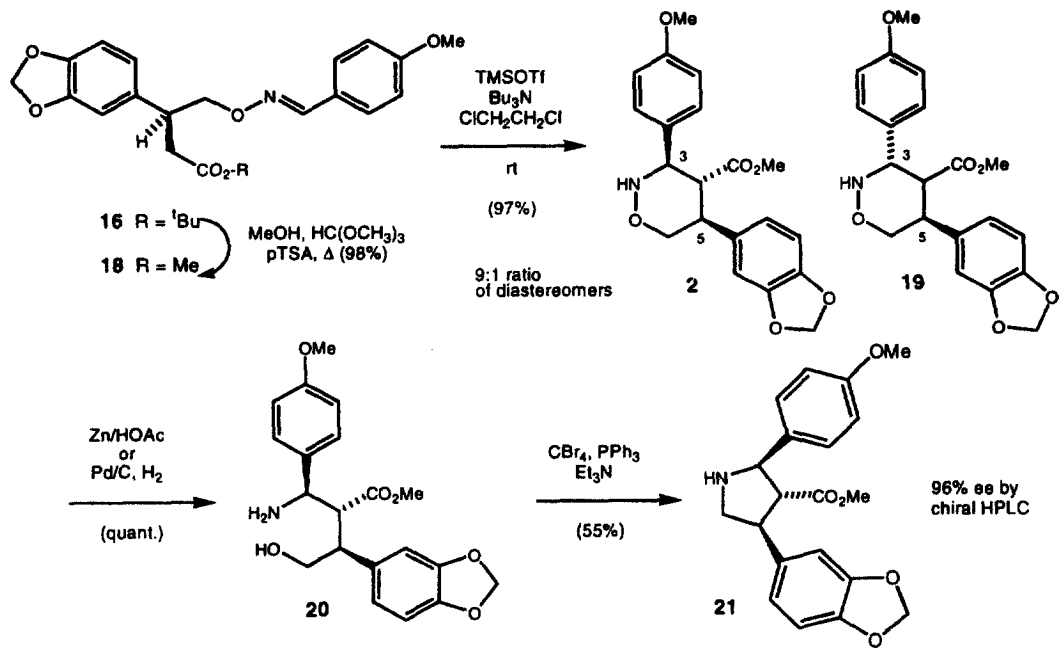


Scheme 3.

For the key reaction, the *t*-butyl ester **16** was not compatible with the cyclization conditions so an exchange to the methyl ester **18** was effected in high yield (Scheme 4). This compound was treated with TMSOTf in the presence of tributylamine at ambient temperature to give diastereomeric 1,2-oxazine products **2** and **19** in a 9:1 ratio; **2** was isolated in 88% yield. The stereochemistry at the two newly formed sp^3 stereocenters was directed by the sole preexisting sp^3 stereocenter, the piperonyl (Pip) bearing carbon (C5), as a consequence of the chair-like transition state **3** (Scheme 1). Of these two new stereocenters, only the configuration of the α-amino carbon (C3) is critical because the ester substituent at C4 could be epimerized from the 3,4,5-*syn* diastereomer to the desired '*trans,trans*' diastereomer. Compound **19** was shown not to be the 3,4,5-*syn* diastereomer; treatment with NaOMe/MeOH at 55°C produced an approximately equal mixture of **19** and a new diastereomer (not **2**) suggesting an *anti* relationship between the aryl substituents.

The N–O bond of the major 1,2-oxazine diastereomer **2** was cleaved in quantitative yield by either dissolving metal reduction (Zn/HOAc–THF) or hydrogenolysis (Pd/C, H_2, EtOH) to produce the diastereomerically pure 2,3,4-trisubstituted-4-aminobutan-1-ol **20**. Cyclization to the pyrrolidine **21** was effected by hydroxyl group activation with triphenylphosphine and carbon tetrabromide.[8] Pyrrolidine **21** was isolated in 55% yield (96% ee by chiral HPLC analysis). The pyrrolidine **21** was converted into ABT-627 (**1**) by *N*-alkylation with *N,N*-dibutyl bromoacetamide followed by ester hydrolysis and salt formation by the previously described procedures.[5]

In summary, we have described a novel cyclization strategy to prepare a 3,4,5-trisubstituted-1,2-oxazine with good diastereocontrol. Reductive N–O bond cleavage produced the substituted 4-aminobutan-1-ol **20** which was cyclized to the pyrrolidine **21**, an intermediate in the synthesis of endothelin antagonist ABT-627 (**1**).



Scheme 4.

Acknowledgements

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