Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 2, pp. 321-324, 1995

0957-4166/95 $9.50+0.00

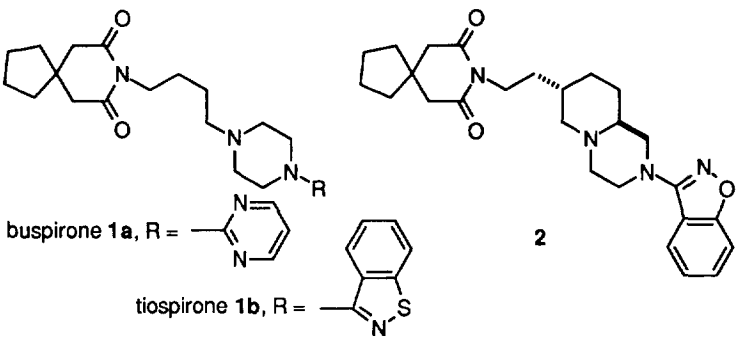
0957-4166(95)00003-8

Synthesis of an Optically Active Octahydro-2H-pyrido[1,2-a]pyrazine Based CNS Agent.

Frank J. Urban*, Ralph Breitenbach, Charles W. Murtiashaw and Brian C. Vanderplas
Pfizer Inc, Central Research Division
Process Research and Development Department
Eastern Point Rd., Groton, Connecticut, 06340

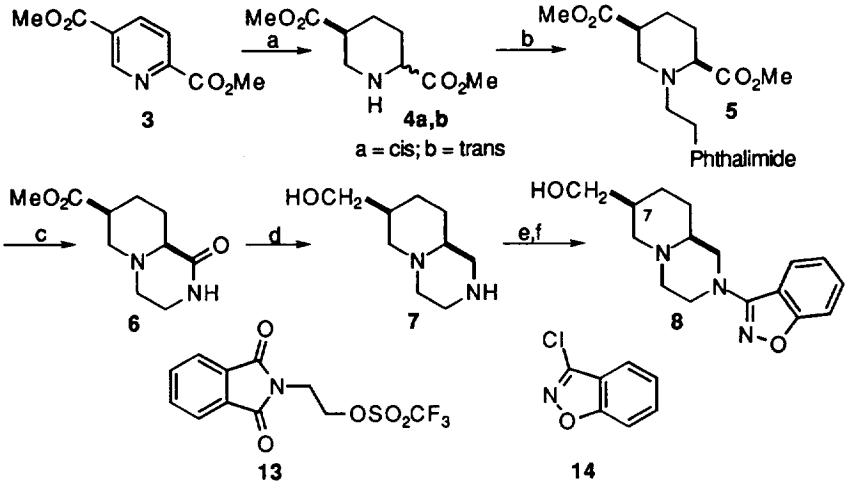
Abstract: A synthesis of an optically active octahydro-2H-pyrido[1,2-a]pyrazine is presented. The key sequence involved the equilibration of an optically active cis-aldehyde to give the thermodynamic trans-aldehyde that was trapped by nitromethane anion.

The synthesis of octahydro-2H-pyrido[1,2-a]pyrazines has been of interest for the study of conformationally restricted analogues of various piperazine based drugs.[1] Within Pfizer Central Research, Dr. Michael Bright has synthesized conformationally restricted analogues related to the serotonergic anxiolytics buspirone[2] **1a** and tiospirone[3] **1b**. In this paper, we describe an efficient synthesis of one of these compounds, 2,7-trans-substituted octahydro-2H-pyrido[1,2-a]pyrazine **2**[4] in optically active form.



The starting material was dimethyl 2,5-pyridine dicarboxylate **3** which was hydrogenated over platinum oxide in acetic acid to provide a 9:1 mixture of cis **4a** and trans **4b** in 90% yield. The cis-7-(hydroxymethyl)-octahydro-2H-pyrido[1,2-a]pyrazine ring system was elaborated in three high yield steps: 1) alkylation of **4** with phthalimidoethyl triflate[5] **13** in a biphasic reaction with aqueous sodium carbonate; 2) removal of the phthalimide group with hydrazine hydrate in methanol; and 3) reduction of **6** with excess lithium aluminum hydride in refluxing tetrahydrofuran. The yield for the overall conversion of **3** to **7** was 62% and the minor trans-piperidine diester **4b** was removed by crystallization after conversion to the mixture of **5a** and **5b** (Scheme 1). The sidechain precursor 3-chlorobenzisoxazole **14** was prepared in two steps from salicylhydroxamic acid.[6] Salicylhydroxamic acid was treated with carbonyldiimidazole in refluxing tetrahydrofuran to provide 3-hydroxy-benzisoxazole in 76% yield.[7] Reaction of 3-hydroxy-benzisoxazole

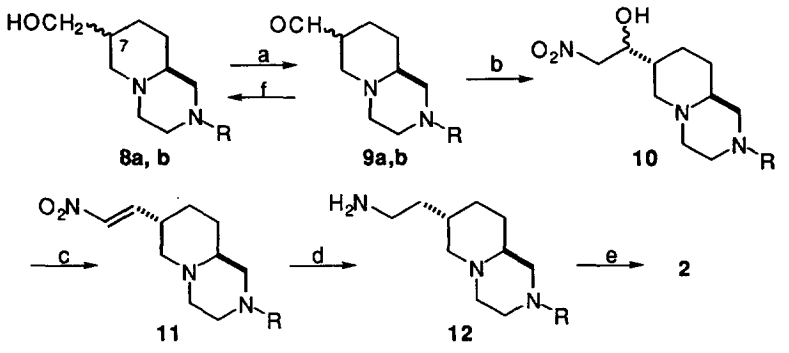
with phosphorus oxychloride in pyridine gave **14** in 88% yield.[8] Alkylation of diamine **7** with 3-chlorobenzisoxazole **14** was achieved in pyridine solution with one equivalent of DBU to provide racemic **8** in 90% yield. In the absence of DBU, the alkylation gave much lower yields of **8**. Diamine **8** proved to be an excellent substrate for classical resolution. Crystallization of the D-(–)-tartaric acid salt of **8**[9] from methanol afforded optically pure material in 45% yield out of the possible 50%.[10]



a) H_2, PtO_2, AcOH, 90%; b)CH_2Cl_2, aqueous Na_2CO_3, **13**, 85%; c) $N_2H_4 \cdot H_2O$, CH_3OH, >90%; d) $LiAlH_4$, tetrahydrofuran, >90%; e) **14**, DBU, pyridine, 90%; f) D (-)-tartaric acid, methanol, 45%.

Scheme 1

With optically active **8** in hand, we needed to invert the stereocenter at C-7 (Scheme 2). This was accomplished in a two step sequence. First, alcohol **8** was oxidized to aldehyde **9** with sulfur trioxide pyridine complex and dimethylsulfoxide in methylene chloride solution in the presence of Hunig's base.[11] Aldehyde **9** was isolated as a white solid in 75% yield after purification via its water soluble bisulfite adduct in order to remove a small amount of a methylthiomethyl ether side product. The NMR spectrum of **9a** in deuteriochloroform showed a small amount of trans-aldehyde **9b** indicating the ease of equilibration. Treatment of **9a** in methanol with a catalytic amount of sodium carbonate caused equilibration of the aldehyde group over several hours to a 15:1 ratio of trans **9b** and cis **9a**. Addition of sodium borohydride to the reaction mixture at this point generated the mixture of trans and cis alcohols from which **8b** was isolated by crystallization from isopropanol and hexanes in 75% yield in optically pure form.[12]



a) C_5H_5N-SO_3, DMSO, Hunig's base, CH_2Cl_2, 75%; b) Na_2CO_3, MeOH, CH_3NO_2, 82%; c) Ac_2O, DMAP, THF, Na_2CO_3, 83%; d) $LiAlH_4$, THF, 45%; e) 3,3-tetramethylene glutaric anhydride, Ac_2O, toluene, 70%; f) Na_2CO_3, $NaBH_4$, MeOH, 75%.

Scheme 2

While **8b** could be used to prepare **2**, a more direct route involved equilibration of aldehyde **9a** as described above followed by addition of several equivalents of nitromethane to the reaction mixture to effect the Henry reaction.[13] The resulting nitroalcohol **10** crystallized from the reaction mixture in 82% yield. By NMR analysis, **10** was a mixture of epimers at the new secondary alcohol center, but consisted of only trans-piperidine isomers as shown. The dehydration of alcohol **10** to nitroolefin **11** was more complicated than anticipated. Activation with acetic anhydride / pyridine[14] or methanesulfonyl chloride / triethylamine[15] failed to give complete conversion. However, reaction of **10** with two equivalents of acetic anhydride and 5 mol% dimethylaminopyridine in tetrahydrofuran solution completely acetylated the alcohol.[16] The reaction mixture was diluted with methanol and one equivalent of sodium carbonate was added to effect elimination to nitroolefin **11** in 83% yield. The reduction of nitroolefin **11** to primary amine **12** was conducted with lithium aluminum hydride in refluxing THF.[17] While the yield for this procedure was only 45%,[18] it did provide material for the completion of the synthesis of **2** to confirm that the material was identical with that prepared by earlier processes. Finally, amine **12** was heated with one equivalent of 3,3-tetramethyleneglutaric anhydride in toluene solution until all the amine was converted to the amide-acid. At this point excess acetic anhydride was added to close the imide ring and complete the synthesis of optically pure **2** in 5% overall yield from dimethyl 2,5-pyridine dicarboxylate. In conclusion, we have presented an efficient synthesis of the octahydro-2H-pyrido[1,2-a]pyrazine **2** that was carried out in good overall yield without any chromatography. This work made available useful intermediates for further studies in this area.

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(*Received in USA* 3 *November* 1994)