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Synthesis of a Potent hNK-1 Receptor Antagonist via an S_N2 Reaction of an Enantiomerically Pure α-Alkoxy Sulfonate

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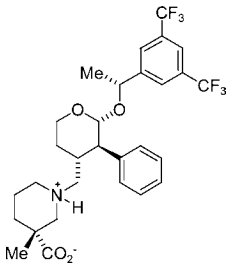
ABSTRACT



The concise synthesis of a stereochemically rich hNK-1 receptor antagonist is described. The synthesis is highlighted by an S_N2 reaction of an enantiomerically pure α-alkoxy sulfonate (orthogonally protected butane triol), which was prepared by utilizing salen-mediated hydrolytic kinetic resolution technology. A stereocontrolled acetalization was employed to connect two enantiomerically pure fragments with a high degree of diastereoselectivity.

The neuropeptide substance P was discovered 70 years ago,[1] characterized in 1970,[2] and has been found to preferentially bind to the human neurokin-1 (hNK-1) receptor.[3] This undecapeptide is concentrated in the central and peripheral nervous system and gastrointestinal tissue.[4] The hNK-1 receptor is involved in a wide array of biological functions, and it has been suggested that modulating the interaction between substance P and the hNK-1 receptor may affect numerous and diverse disease states,[5] which has prompted the search for selective hNK-1 receptor antagonists. Tetrahydropyran **1** has been identified as one such selective hNK-1 receptor antagonist.[6] This target molecule contains five stereocenters, none of which is readily accessible from chiral pool starting materials. The central core possesses three all-*trans* contiguous stereocenters: one of these is a mixed acetal and all three substituents are equatorial. The southern fragment is a quaternary substituted piperidine, and the northern fragment consists of an electron-deficient, stereochemically defined benzylic ether. Viewing **1** as containing

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(1) Von Euler, U. S.; Gaddum, J. H. *J. Physiol.* **1931**, *72*, 74.
(2) Chang, M. M.; Leeman, S. E.; Niall, H. D. *Nat. New Biol.* **1971**, *232*, 86.
(3) Guard, S.; Watson, S. P. *Neurochem. Int.* **1991**, *18*, 149.
(4) Nicoll, R. A.; Schenker, C.; Leeman, S. E. *Annu. Rev. Neurosci.* **1980**, *3*, 227.
(5) For reviews, see: (a) Takeuchi, Y.; Shands, E. F. B.; Beusen, D. D.; Marshall, G. R. *J. Med. Chem.* **1998**, *41*, 3609. Otsuka, M.; Yoshioka, K. *Physiol. Rev.* **1993**, *73*, 229. (c) Maggi, C. A.; Patacchini, R.; Rovero, P.; Giachetti, A. *J. Auton. Pharmacol.* **1993**, *13*, 23. (d) Longmore, J.; Swain, C. J.; Hill, R. G. *Drug News Perspect.* **1995**, *8*, 5. (e) Regoli, D.; Boudon, A.; Fauchere, J.-L. *Pharmacol. Rev.* **1994**, *46*, 551. (f) MacLean, S. *Med. Res. Rev.* **1996**, *16*, 297. (g) Lowe, J. A., III. *Med. Res. Rev.* **1996**, *16*, 527. (h) Barker, R. *Neurosci. Rev.* **1996**, *7*, 187.
(6) Owen, S. N.; Seward, E. M.; Swain, C. J.; Williams, B. J. U.S. Patent 6,458,830 B1, 2001.

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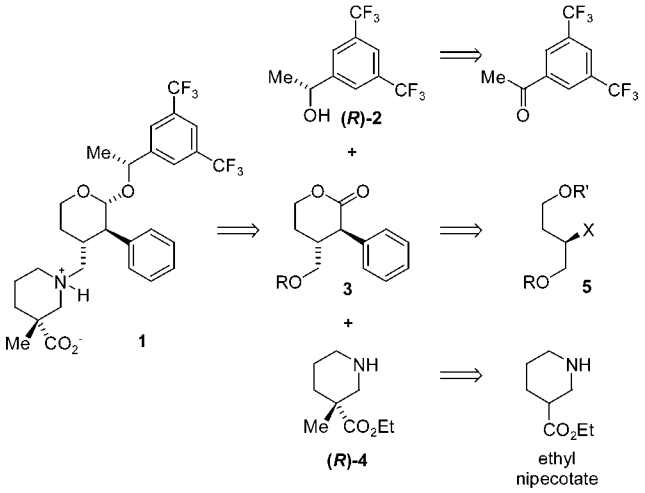
an anomeric carbon leads to two attractive disconnections. These scissions would allow for the convergent assembly of **1** by coupling a derivative of the central core unit **3** with two excised enantiomerically pure fragments, alcohol **2** and piperidine **4** (Scheme 1). Chiral alcohol **2** could be obtained

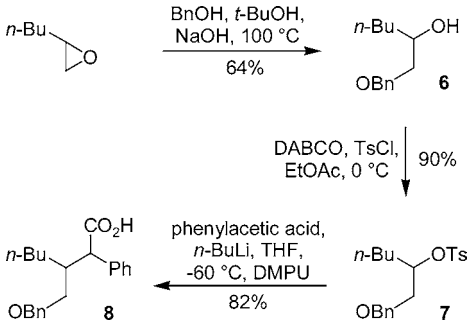
Scheme 1. Retrosynthetic Analysis



from the asymmetric reduction of the corresponding ketone,[7] and the quaternary substituted piperidine **4** potentially could be derived from ethyl nipecotate.

One possible asymmetric approach to lactone **3** hinged on the stereospecific displacement of a leaving group from a secondary center of electrophile **5** with the enolate of a phenylacetate derivative (Scheme 1).[8] Although 2-arylalkanoic acids have recently been prepared by the alkylation of carboxylate enolates with tosylates,[9] it was not apparent whether enantiomerically pure, α-alkoxy secondary tosylates would enter into this protocol; concerns included low substrate reactivity, stereocenter scrambling, and elimination. To investigate the effect of the neighboring alkoxyl group on the electrophile, tosylate **7** was synthesized from 1,2-epoxyhexene (Scheme 2). The lithium dianion of phenylacetic acid cleanly displaced the tosyl group of **7** to afford the desired α-phenyl-*β*-alkoxymethyl carboxylic acid **8** in an 82% isolated yield. This indicated that an adjacent alkoxy

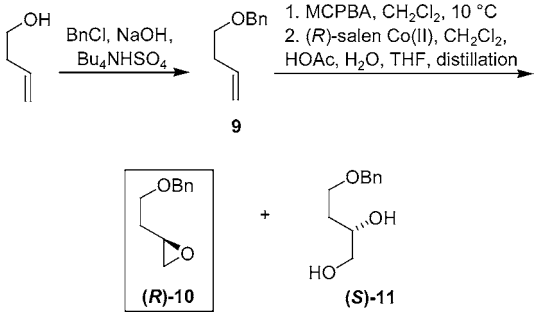
Scheme 2. α-Alkoxy Sulfonate Displacement



or aryloxy group should not significantly prohibit a substitution reaction of the fully elaborated electrophile.

Toward this end, tosylate (*R*)-**13**, an orthogonally protected butane triol, was targeted. The first step of this synthesis was accomplished by alkylation of 3-butene-1-ol with BnCl under solvent-free phase transfer catalysis conditions (NaOH/BnCl/Bu_4NHSO_4)[10] to afford benzyl ether **9** (Scheme 3).[11]

Scheme 3. HKR Synthesis of Epoxide (*R*)-**10**



A small amount of the symmetric ether (BnOBn) was formed in this process, which was suppressed by using more concentrated NaOH.

Treatment of alkene **9** with *m*-chloroperbenzoic acid cleanly afforded racemic epoxide **10**,[12] which readily underwent a salen-mediated (1.5 mol % catalyst, 50 mol % H_2O) hydrolytic kinetic resolution.[13] The desired epoxide (*R*)-**10**[14] was conveniently separated from the newly formed diol antipode (*S*)-**11** by distillation. Chiral SFC indicated that the enantiomeric ratio of the isolated epoxide **10** was >99:1 (*R*:*S*). Subsequent oxirane ring opening was accomplished with 4-methoxyphenol (PMP-OH) and K_2CO_3, which proved to be much cleaner than the similar openings with sodium and potassium alkoxides of aliphatic alcohols (Scheme 2).[15]

(7) Hansen, K. B.; Chilenski, J. R.; Desmond, R.; Devine, P. N.; Grabowski, E. J. J.; Heid, R.; Kubryk, M.; Mathre, D. J.; Varsolona, R. *Tetrahedron*: *Asymmetry* **2003**, *14*, 3581.

(8) For recently developed alternative asymmetric methodology for the preparation of 3-aryl-*δ*-lactones, see: (a) Smitrovich, J. H.; Boice, G. N.; Qu, C.; DiMichele, L.; Nelson, T. D.; Huffman, M. A.; Murry, J.; McNamara, J.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1963. (b) Smitrovich, J. H.; DiMichele, L.; Qu, C.; Boice, G. N.; Nelson, T. D.; Huffman, M. A.; Murry, J. *J. Org. Chem.* **2004**, *69*, 1903.

(9) Kusumoto, T.; Ichikawa, S.; Asaka, K.; Sato, K.-i.; Hiyama, T.; *Tetrahedron Lett.* **1995**, *36*, 1071.

(10) (a) Freedman, H. H.; Dubois, R. A. *Tetrahedron Lett.* **1975**, *16*, 3251. (b) Burgstahler, A. W.; Weigel, L. O.; Sanders, M. E.; Shaefer, C. G.; Bell, W. J.; Vuturo, S. B. *J. Org. Chem.* **1977**, *42*, 566.

(11) For alternative preparations of 4-benzyloxy-1-butene (**9**), see: (a) Westwell, A. D.; Williams, J. M. J. *Tetrahedron* **1997**, *53*, 13063. (b) Berranger, T.; Langlois, Y. *J. Org. Chem.* **1995**, *60*, 1720.

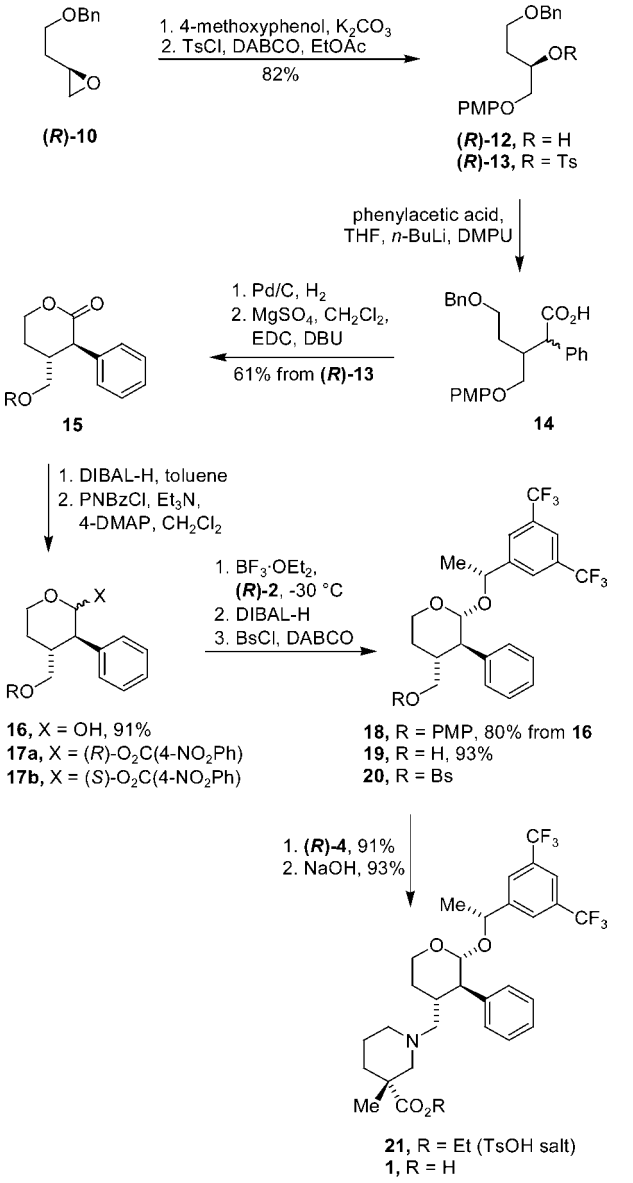
(12) (a) Muehlbacher, M.; Poulter, C. D. *J. Org. Chem.* **1988**, *53*, 1026.

(13) (a) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307. (b) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421.

(14) For an alternative synthesis of (*R*)-**10**, see: Frick, J. A.; Klassen, J. B.; Bathe, A.; Abramson, J. M.; Rapoport, H. *Synthesis* **1992**, 621.

(15) We synthesized and utilized other orthogonally substituted triols; however, these strategies suffered from either poor epoxide opening yields, low downstream yields, or significant problems relating to acetal decompostion during subsequent deprotection. The use of the PMP protecting group for the primary alcohol successfully overcame these issues. Fukuyama, T.; Laird, A. A.; Hotchkiss, L. M. *Tetrahedron Lett.* **1985**, *26*, 6291.

Scheme 4. Synthesis of hNK-1 Receptor Antagonist **1**



The HPLC assay yield was typically 90−95%, and the excess phenol was removed by simple caustic extractions. Activation of the resulting alcohol (*R*)-**12** with TsCl/DABCO[16] cleanly and rapidly formed the desired, highly crystalline tosylate (*R*)-**13**. This valuable orthogonally protected, enantiomerically pure butanetriol electrophile was stored at room temperature for more than 1 year without evidence of decomposition.

The alkylation of the tosylate (*R*)-**13** with the dilithium salt of phenylacetic acid (1.25 equiv) cleanly (>99 HPLC area percent) afforded the substituted product **14** (6:1 diastereomeric ratio by ^{1}H NMR). Elimination of the tosylate was not observed. Excess phenylacetic acid and the TsOH byproduct were selectively extracted from the reaction mixture by two $NaHCO_3$ washes. A through process for the conversion of tosylate (*R*)-**13** to the *trans*-lactone **15** (isolated as a crystalline solid) was then developed. Initially, the hydrogenation of benzyl ether **14** was performed in EtOH; however, ethyl ester contaminants were formed. Ambient pressure hydrogenation of **14** in EtOAc cleanly converted the benzyl ether to a mixture of corresponding primary alcohol (ca. 90:10 *syn*/*anti*) and lactone **15** (78:22 *cis*/*trans*). A desiccant ($MgSO_4$) was added to the crude slurry followed by the addition of 60 mol % EDC. After lactonization was complete, the crude mixture was filtered, and the resulting product stream was epimerized with catalytic DBU to afford a 94:6 ratio of *trans*/*cis* lactones **15** from which *trans*-lactone **15** was crystallized. Overall, enantiomerically pure tosylate (*R*)-**13** was converted to enantiomerically pure *trans*-lactone **15** (*cis*/*trans* = 0.2:99.8) as a white crystalline solid in 61% yield.

Reduction of this lactone afforded lactol **16**, which was also isolated as a white solid. Lactol activation gave a >98% HPLC assay yield of the PNBz derivative **17**. BF_3·OEt_2-mediated coupling of this activated lactol with alcohol (*R*)-**2** afforded an anomeric mixture of acetals **18** and **22** (Figure 1). An important feature of this acetalization was that the anomer ratio (*R*:*S*) decreased with time, indicating that the product mixture was establishing a thermodynamic isomeric ratio. In fact, allowing the reaction to age for 13 h at −30 °C resulted in an 86:14 (**18**:**22**) ratio, whereas an aliquot after only 10 min gave a 90:10 ratio of diastereomers. This was further substantiated by resubjecting authentic diastereomerically pure **22** to BF_3·OEt_2 at room temperature. This afforded an 81:19 ratio of **18** to **22** (*RRRR*:*RRSR*), along with 5% of eliminated product **23** (Figure 1). These results indicate that the initial carbon−oxygen bond formation is operating under kinetic control and that the thermodynamically favored product ratio is established upon aging the reaction mixture. In addition, it was not necessary to utilize diastereomerically pure nitrobenzoate **17a** in the Lewis acid mediated coupling reaction. The same ratio of diastereomers was obtained from the coupling reaction regardless of the diastereomeric purity of the anomeric center in the precursor nitrobenzoate **17**. Both 99:1 [**17a**:**17b**] and 90:10 [**17a**:**17b**] samples of the nitrobenzoate independently gave an identical 92:8 ratio of acetals [**18**:**22**] (Scheme 5). This suggests that the reaction proceeds via an oxonium ion intermediate.

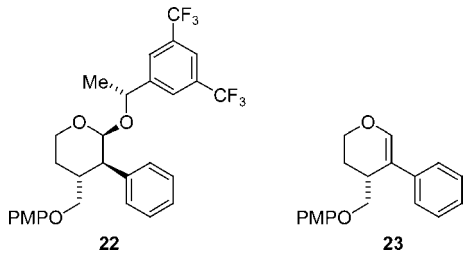
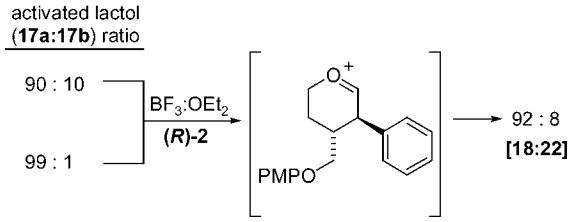


Figure 1.

A typical procedure entailed quenching the BF_3·OEt_2 reaction mixture immediately after acetal formation. This was

(16) Hartung, J.; Hunig, S.; Kneuer, R.; Schwarz, M.; Wenner, H. *Synthesis* **1997**, 1433.

Scheme 5. Acetalization



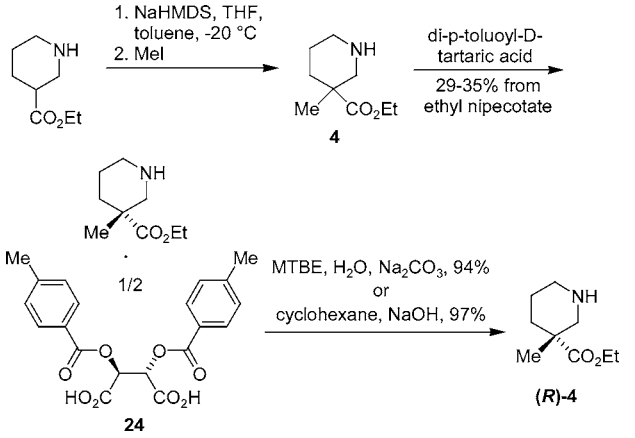
followed by a selective crystallization of acetal **18** from the diastereomeric reaction mixture that contained 8% *cis* acetal **22**. The resulting stable crystalline acetal **18** was then successfully deprotected (CAN, 4:1 CH_3CN/H_2O) to give a mixture of **19** and benzoquinone. After dilution of the deprotection reaction mixture with MTBE, aqueous caustic washes were successful in partitioning the desired primary alcohol **19** and the benzoquinone waste. A stream of alcohol **19** was then activated with benzenesulfonyl chloride, and the resulting besylate **20** was displaced with the chiral nipecotate derivative (*R*)-**4**.

The synthesis of piperidine (*R*)-**4** was accomplished by first alkylating ethyl nipecotate with NaHMDS and MeI with a high level of selectivity.[17] The ratio of desired C-alkylation to both N-alkylation and C,N-dialkylation was >98:1:1 (GC analysis of unpurified reaction mixture) (Scheme 6). Racemic amine **4** was resolved with di-*p*-toluoyl-D-tartaric acid to form a high-melting 2:1 crystalline salt **24** in 35% overall yield (70% of theory) in >97% ee. A simple salt break provided enantiomerically pure piperidine (*R*)-**4**.

Besylate **20** and amine (*R*)-**4** were coupled to form the tertiary amine, which was isolated as the crystalline tosylate salt **21**. Saponification of carboethoxy moiety of penultimate

(17) For benzylation of ethyl nipecotate via a similar protocol, see: Maligres, P. E.; Chartrain, M. M. Upadhyay, V.; Cohen, D.; Reamer, R. A.; Askin, D.; Volante, R. P.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 9548.

Scheme 6. Ethyl 3-Methylpiperidine-3-carboxylate (*R*)-**4**



tosylate salt **21** cleanly afforded the desired hNK1 receptor antagonist **1** as a crystalline solid.

Overall, we have demonstrated a concise synthesis of the stereochemically rich hNK-1 receptor antagonist **1**. The synthesis is highlighted by an S_N2 reaction of an enantiomerically pure α-alkoxy sulfonate. The stereochemistry of this orthogonally protected butane triol was established by a salen-mediated hydrolytic kinetic resolution. The central core was then coupled to alcohol (*R*)-**2** via a stereocontrolled acetalization.

Acknowledgment. The authors thank Dr. Brian J. Williams for helpful discussions during the development of this work.

Supporting Information Available: Experimental procedures and characterization data for compounds **1**, (*R*)-**13**, **15**, **16**, **18**, **21**, **23**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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