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Design and Synthesis of Novel Scaffolds for Drug Discovery: Hybrids of β-D-Glucose with 1,2,3,4-Tetrahydrobenzo[e][1,4]diazepin-5-one, the Corresponding 1-Oxazepine, and 2- and 4-Pyridyldiazepines

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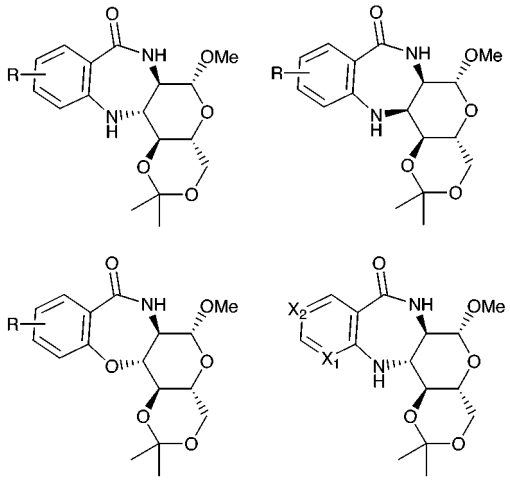
ABSTRACT



We describe the syntheses of novel tricyclic scaffolds that incorporate a fusion of a substituted pyranose ring with the seven-membered rings of 1,2,3,4-tetrahydrobenzo[*e*][1,4]diazepin-5-one and the corresponding oxazepine and pyridyldiazepine to generate the benzodiazepines, and the related heterocycles. In each instance, the pyranose rings contain three protected hydroxyls, suitable for selective derivatization.

Privileged Scaffolds in Drug Discovery. The search for new medicines continues to depend on the discovery of new leads, uncovered either via rationally designed chemical entities or the screening of sample collections, increasingly generated by combinatorial or parallel syntheses. The design of such libraries may involve novel scaffolds to which diverse side chains are attached, the trajectories of which seek to explore three-dimensional space. An important overlapping principle is the concept of privileged (or promiscuous) structures, recently updated by Patchett.[1] The former term was introduced by B. Evans et al.,[2] as a descriptor that recognizes the fact that seemingly minor changes in the structures of

(1) Patchett, A. A.; Nargund, R. P. *Ann. Rep. Med. Chem.* **2000**, *35*, 289.

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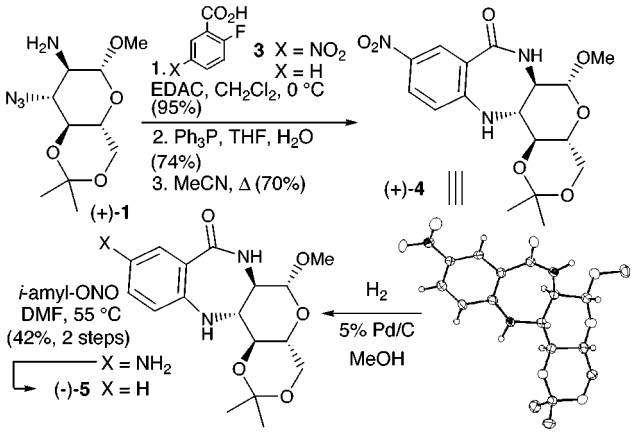
benzodiazepines can produce a host of different biological activities, which now include not only ligands for diverse G-protein coupled receptors but also inhibitors of enzymes such as reverse transcriptase,[3] farnesyl transferase, κ-secretase, and dihydrofolate reductase, as well as ligands for ion channels. In the 1960s the so-called tricyclic scaffold,[4] as found in protriptyline, was similarly recognized to be associated with diverse biological activities, depending on the attached side chains and other modifications.[5] Long ago, Nature herself discovered privileged structures such as the steroidal and the cyclic peptide scaffolds, as well as β-turns and helices, etc. We have suggested[6] that in addition to incorporated heteroatoms, the side chain projections of privileged ligand platforms, which include β- and γ-turns, their components or their mimics, are recognized by common structural motifs in G-protein coupled receptors, which make these receptors complementary to the privileged platforms. Although to our knowledge, no unifying three-dimensional structural feature for privileged structures has been identified, the lack of planarity present in the benzodiazepines suggested itself as a possibility because it permits the exploration of increased conformational space. Herein we describe the design and synthesis of new scaffolds that are hybrids of benzodiazepines, oxazepines and pyridyldiazepines with sugars, wherein the latent hydroxyl groups of the pyranose ring permit diverse, controlled derivatization at three sites.

The Chimeric Benzodiazepine−Sugar Scaffold.[7] Our initial approach[8] toward the chimeric 1,4-benzodiazepin-5-one−sugar system[9] (Scheme 1) entailed acylation of (+)-**1**,

Scheme 1



prepared from (−)-**2**,[10] with acid **3** (X = H), followed in turn by azide reduction to afford the amine and ring closure to produce the 1,4-benzodiazepin-5-one ring (Scheme 1). Unactivated (X = H) *o*-halide-substituted benzamides,[11] however, failed to undergo ring closure under both thermal and transition metal mediated conditions. We therefore explored the synthesis of an activated precursor possessing a *para*-nitro group obtained via coupling (+)-**1** with 2-fluoro-5-nitrobenzoic acid **3** (X = NO_2). Staudinger reduction[12] of the resulting azide yielded the amine, which upon heating at 80 °C for 48 h in anhydrous acetonitrile furnished the yellow, crystalline 1,4-benzodiazepin-5-one (+)-**4** (mp 150−152 °C) in 70% yield; the structure was confirmed by single-crystal X-ray analysis. Dimer formation was observed when the reaction was carried out at concentrations above 0.005 M. Importantly, (+)-**4** possesses good cell permeability properties with a log $P = 2.53$, a high P_{app} value [17×10^{-6}] across Caco-2 cells[13] and adequate solubility properties [crystalline (+)-**4**: H_2O 0.610 mg/mL; pH 7.4 buffer 0.54 mg/mL; 0.10 N HCl 5.073 mg/mL]. Reductive removal of the nitro group utilizing the diazotization procedure of Doyle[14] afforded the parent congener (−)-**5** in 42% yield for the two steps.

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(3) (a) Robl, J. A.; Cimarusti, M. P.; Simpkins, L. M.; Brown, B.; Ryono, D. E.; Bird, E.; Asaad, M. M.; Schaeffer, T. R.; Trippodo, N. C. *J. Med. Chem.* **1996**, *39*, 494−502. (b) De Lombaert, S.; Beil, M.; Berry, C.; Blanchard, L.; Bohacek, R.; Chatelin, R.; Gerlock, T.; Ghai, R. D.; Odorico, L.; Sakane, Y.; Stamford, L. B.; Trapani, A. J. *Abstracts of Papers*, 212th National Meeting of the American Chemical Society, Orlando, FL; American Chemical Society: Washington, DC, 1996; MEDI 12. (c) Merluzzi, V. J.; Hargrave, K. D.; Labadia, M.; Grozinger, K.; Skoog, M.; Wu, J. C.; Shih, C.-K.; Eckner, K.; Hattox, S.; Adams, J.; Rosenthal, A. S.; Faanes, R.; Eckner, R. J.; Koup, R. A.; Sullivvan, J. L. *Science* **1990**, *250*, 1411−1413.

(4) Ariëns, E. J.; Beld, A. J.; Rodrigues de Miranda, J. F.; Simonis, A. M. In *The Receptors: A Comprehensive Treatise*; O' Brien, R. D., Ed.; Plenum: New York, 1979; pp 33−91.

(5) Davis, M. A. *Ann. Rep. Med. Chem.* **1968**, *2*, 13.

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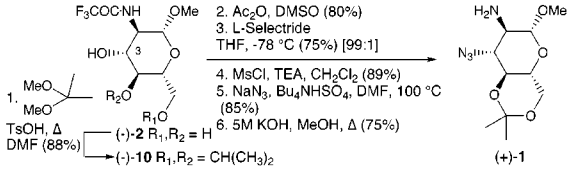
(7) Presented in part: Abrous, L.; Hynes, J., Jr.; Friedrich, S. R.; Smith, A. B., III; Hirschmann, R. *Abstracts of Papers*, 220th National Meeting of the American Chemical Society, Washington, DC; American Chemical Society: Washington, DC, 2000; MEDI 254.

(8) Hynes, John, Jr., Ph.D. Dissertation, University of Pennsylvania, Philadelphia, PA, 1996. See also: Woolard, F. X.; Paetsch, J.; Ellman, J. A. *J. Org. Chem.* **1997**, *62*, 6102−6103.

(9) *Bicyclic Diazepines*; Fryer, R. Ian, Ed.; John Wiley and Sons: New York, 1991; pp 183−946.

(10) Available from the known triol (−)-**2** [Midoux, P.; Grivet, J. P.; Delmotte, F.; Monsigny, M. *Biochem. Biophys. Res. Comm.* **1984**, *119*, 603] via dimethylacetal protection to afford (−)-**10** (step 1) followed by double inversion at C(3):



(11) Further investigation into transition metal mediated heteroaryl bond formation methodologies may provide a possible alternative entry into the tricyclic system. Using Pd: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35. (c) Rocca, P.; Marsais, F.; Godard, A.; Quenguiner, G. *Tetrahedron* **1993**, *49*, 49. (d) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348. Using Cu: (e) Lindley, J. *Tetrahedron* **1984**, *40*, 1433. Takei, T.; Matsuoka, M.; Kitao, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2735. Matsuoka, M.; Makino, Y.; Yoshida, K.; Kitao, T. *Chem. Lett.* **1979**, 219.

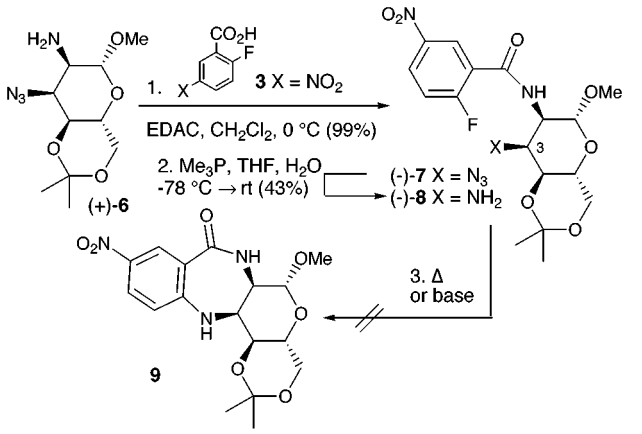
(12) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635.

(13) An in vitro cell culture model of the intestinal mucosa. Apical to basolateral flux of (+)-**4** was measured. For a review see: Pauletti, G. M.; Gangwar, S.; Siahaan, T. J.; Aubé, J.; Borchardt, R. T. *Adv. Drug Delivery Rev.* **1997**, *27*, 235.

(14) (a) Doyle, M. P.; Dellaria, J. F., Jr.; Siegfried, B.; Bishop, S. W. *J. Org. Chem.* **1977**, *42*, 3494.

We next envisioned ready access to the cis-fused sugar-benzodiazepine **9** via a parallel sequence (Scheme 2). Toward

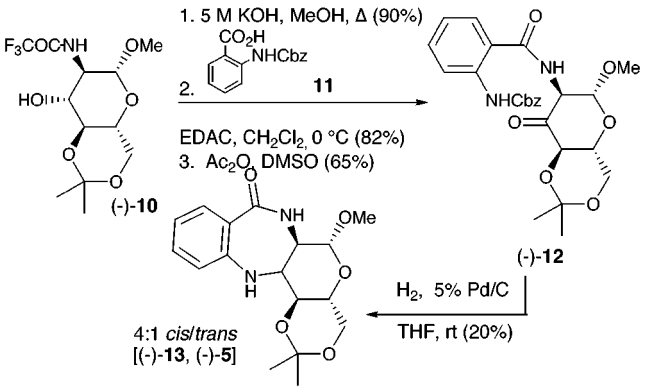
Scheme 2



this end, reaction of the C(3) axial azide (+)-**6**[15] afforded (−)-**7**. Interestingly, reduction of (−)-**7** with triphenylphosphine proved unsuccessful. The smaller, more reactive trimethylphosphine did, however, furnish (−)-**8**. Unfortunately, cyclization of (−)-**8** to the cis-fused scaffold **9** proved unsuccessful when the reaction was either heated or treated with a variety of bases under varied temperature and solvent conditions.

Our attention therefore turned toward a one-pot protocol, involving first unmasking the aniline in (−)-**12**, followed by intramolecular imine formation with concomitant reduction to furnish the cis- and trans-fused benzodiazepine−sugar scaffolds. We began this sequence with removal of the trifluoroacetamide group in (−)-**10**[9] (Scheme 3), followed

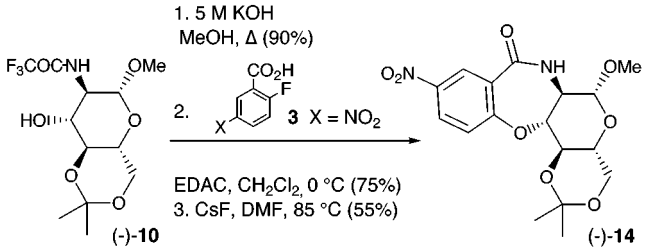
Scheme 3



in turn by selective coupling with *N*-benzyloxycarbonyl (Cbz)-protected anthranilic acid **11** and oxidation of the C(3) hydroxyl to yield (−)-**12**. Catalytic hydrogenation of (−)-**12** then effected removal of the Cbz group, which was followed by cyclization and reduction of the resultant imine. Preferential reduction from the pseudoequatorial face of the strained intermediate cyclic imine afforded the cis-fused benzodiazepine-sugar (−)-**13** as the major product [4:1 cis/trans], in an as yet unoptimized yield (20%), along with the intermediate anilino-ketone, which could be recycled.

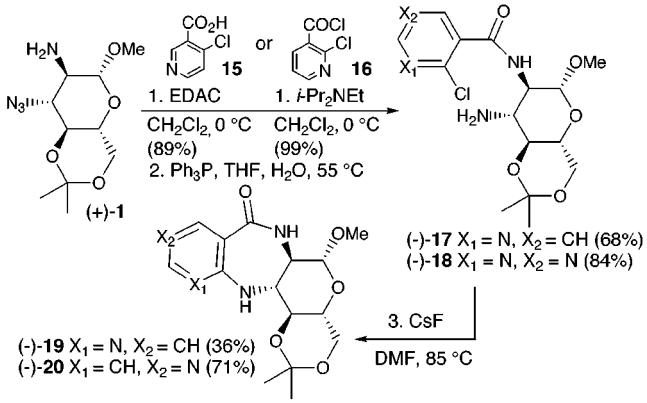
The Chimeric Oxazepine−Sugar Scaffold. Removal of the protecting group in (−)-**10**, followed by coupling with **3** (X = NO_2) and cyclization using CsF as a base in DMF at 85 °C gave (−)-**14** in 55% yield (Scheme 4).

Scheme 4



The Chimeric Pyridyldiazepine−Sugar Scaffolds. Similarly, the isomeric 2- and 4-pyridyldiazepine-sugar scaffolds (−)-**19** and (−)-**20** (Scheme 5) were obtained via cyclization

Scheme 5



of the corresponding 2- and 4-chloro acyl pyridine intermediates (−)-**17** and (−)-**18**. No reaction was observed in absence of CsF; presumably the reaction pathway involves a precedented in situ *ipso*-substitution[16] of the acyl chloride to give the more reactive acyl fluoride.

Having secured synthetic access to each of the chimeric scaffolds, derivatives possessing a variety of side chains were synthesized for broad screening; their biological evaluation is underway at DuPont Pharmaceuticals Co. Optimization of the one-pot cascade for the synthesis of the cis-fused scaffold is also ongoing. Finally, we are exploring the

(15) Available from alcohol (−)-**10** by simple inversion (see ref 10, steps 4, 5, and 6).

(16) Finger, G. C.; Kruse, C. W. *J. Am. Chem. Soc.* **1956**, *78*, 6034.

potential inherent in the design of these scaffolds for subsequent multisite functionalization via parallel synthesis both in solution and on solid supports.

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Supporting Information Available: Spectroscopic and analytical data for intermediates leading to and including (+)-**4** from (−)-**2**, (−)-**13**, (−)-**14**, (−)-**19**, and (−)-**20** and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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