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Synthesis of Aza-, Oxa-, and Thiabicyclo[3.1.0]hexane Heterocycles from a Common Synthetic Intermediate

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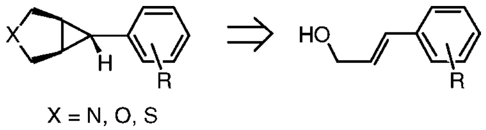
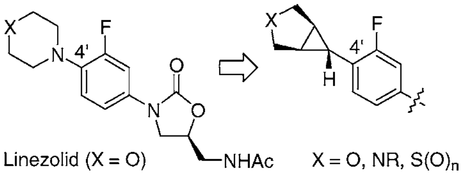
ABSTRACT



An efficient and stereospecific approach to the synthesis of structurally constrained aza-, oxa-, and thiabicyclo[3.1.0]hexane heterocycles has been achieved through application of the intramolecular cyclopropanation reaction of diazoacetates. The various constrained heterocycles (X = N, O, or S) are conveniently prepared from a common diol intermediate accessible from readily available cinnamyl alcohols. Application of the methodology to the synthesis of conformationally constrained oxazolidinone antibacterials is also discussed.

A common strategy in the practice of medicinal chemistry is the introduction of conformational constraint in the design of new inhibitor structures.[1] The goal is tighter and/or more selective binding of the inhibitor to its target. Reducing the entropic costs of binding can produce the desired effect, but only if enthalpically important contacts are not lost as a result of the structural constraint. The most common tactic toward these ends involves the construction of cyclic isosteres of acyclic structures.[1a,b] The further constraint of *cyclic* structures can be achieved through the introduction of unsaturation, through fusion to a second ring, or by conversion of a (mono)cyclic system into a bicyclic one.[1c,d] In this letter, we report a new example of the latter approach and expect that the constrained bicyclic heterocycles described may find application in other lead optimization efforts.

Linezolid (Zyvox) is the first approved antibacterial compound in the new oxazolidinone class of bacterial protein synthesis inhibitors.[2] As part of our efforts to discover novel antimicrobial oxazolidinones with improved properties, we were interested in analogues bearing various bicyclo[3.1.0]hexyl heterocycles at the 4′-position of the aryl ring (as shown below). Such analogues may be viewed as conformationally constrained isosteres of well-known morpholine-, thiomorpholine-, or piperazine-substituted phenyloxazolidinones.



A survey of the literature revealed no general synthetic method that could provide all three heterobicyclic ring systems with the desired substitution patterns. The thiabicyclo[3.1.0]hexane ring system has been prepared by the reaction of 3,3-dimethylpenta-1,4-diene with sulfur dioxide.[3] The

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[1] For recent examples, see: (a) Hanessian, S.; MacKay, D. B.; Moitessier *J. Med. Chem.* **2001**, *44*, 3074. (b) Dutta, A. K.; Davis, M. C.; Reith, M. E. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2337. (c) Ullrich, T.; Binder, D.; Pyerin, M. *Tetrahedron Lett.* **2002**, *43*, 177. (d) Kolhatkar, R.; Cook, C. D.; Ghorai, S. K.; Deschamps, J.; Beardsley, P. M.; Reith, M. E. A.; Dutta, A. K. *J. Med. Chem.* **2004**, *47*, 5101.

[2] Reviews: (a) Brickner, S. J. *Curr. Pharm. Des.* **1996**, *2*, 175. (b) Hutchinson, D. K. *Curr. Top. Med. Chem.* **2003**, *3*, 1021−1042. (c) Nilius, A. M. *Curr. Opin. Invest. Drugs* **2003**, *4*, 149.

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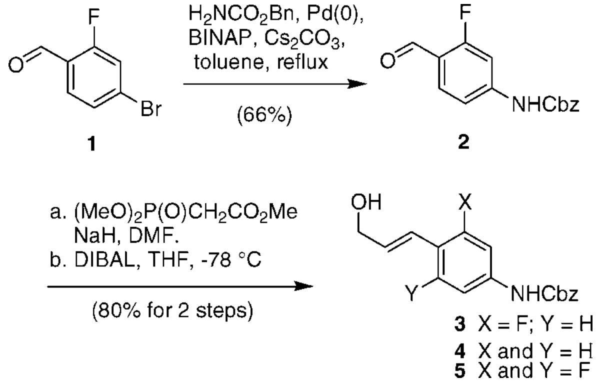
generality of this approach seemed questionable; furthermore, it could not provide access to the oxa- or azabicyclic heterocycles. The azabicyclo[3.1.0]hexane[4] ring system has been prepared through intermolecular cyclopropanation of 3-pyrroline or maleimide substrates.[5] Unfortunately, these reactions often produce mixtures of *exo* and *endo* diastereomers and, furthermore, could not provide ready access to the desired *aryl*-substituted cyclopropanes. We reasoned that an approach involving the well-known intramolecular cyclopropanation of allylic diazoacetates might prove to be more fruitful.[6] It seemed clear that the bicyclic lactones formed in the cyclopropanation reaction could be elaborated into all three heterobicyclic ring systems, although such conversions had not been described previously in the literature. In fact, this approach did prove to be successful and here we disclose the results of our efforts.

The preparation of allylic diazoacetates from allylic alcohols is well precedented.[7] Hence, our initial objective was the preparation of cinnamyl alcohol substrates appropriately substituted for eventual elaboration into the desired oxazolidinone analogues. The cyclopropanation reaction of allylic diazoacetates is a stereospecific reaction, with olefin geometry determining the relative configuration about the cyclopropane ring in the product. A *trans*-olefin is required to produce the desired *exo*-substituted bicyclic ring system, and so we targeted the synthesis of cinnamyl alcohols **3**−**5** (differing only in the extent of fluorination on the aromatic ring). A short and efficient synthesis of alcohol **3** was devised involving as a key step the palladium-catalyzed coupling[8] of aryl bromide **1** and benzyl carbamate. The reaction is scalable, and more than 70 g of **3** were prepared in this fashion (Scheme 1). Similar synthetic routes provided des-fluoro and bis-fluoro intermediates **4** and **5**, respectively (see Supporting Information).

Scheme 1. Synthesis of Cinnamyl Alcohol Intermediate **3**



For the synthesis of the diazo esters, we employed a modification of literature procedures. Specifically, we found it convenient to generate the acid chloride of glyoxylic acid *p*-toluenesulfonylhydrazone in situ by reaction of the acid[7a] with 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine[9] in dichloromethane. Upon fomation of the acid chloride, the cinnamyl alcohol (e.g., **3**) was added, followed by *N*,*N*-dimethylaniline and triethylamine according to Corey and Myers' modification[7b] of the original House procedure.[7a] Using this one-pot procedure, diazoester **6** was prepared in excellent overall yield from alcohol **3** (Scheme 2). Slow addition of diazoester **6** to a refluxing toluene solution of copper catalyst **11**[10] (5 mol %) then provided the racemic *exo*-lactone **7** in good yield.[11] Reduction of **7** to the achiral diol **8** was accomplished in high yield using lithium borohydride in tetrahydrofuran. Notably, the use of other reducing agents produced varying amounts of lactol side product and significantly lowered the isolated yield of **8**. The des-fluoro and bis-fluorophenyl diols **9** and **10** were prepared from **4** and **5**, respectively, using analogous procedures.

With the key diol intermediates **8**−**10** in hand, we addressed their conversion into the desired bicyclo[3.1.0]-hexyl heterocycles, as summarized in Table 1. For thia- and azabicyclic systems, we envisioned that activation of both hydroxyl functions followed by reaction with amine or sulfur nucleophiles would provide the desired heterocycles via an alkylation/cyclization cascade.

For the activation step, mesylation proved to be most convenient, and the use of methanesulfonic anhydride was found to be superior to methanesulfonyl chloride for this purpose. The bis-mesylates of diols **8**−**10** were isolated by extractive workups and generally used without further purification.

For the synthesis of the thiabicyclo[3.1.0]hexyl ring system, the reaction of sodium sulfide with the bis-mesylate[12] in a polar aprotic solvent proved to be quite effective. The reaction occurs cleanly at ambient temperatures without the formation of disulfides or oligomeric side products. Overall yields for the two-step synthesis of thiabicyclic compounds **12**−**14** from diols **8**−**10** were in the range of 79−88%. The reaction proceeded smoothly irrespective of aromatic ring substitution, and the scope of the process is likely to be quite broad.

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(3) Roulet, J.-M.; Deguin, B.; Vogel, P. *J. Am. Chem. Soc.* **1994**, *116*, 3639.

(4) For a review, see: Krow, G. R.; Cannon, K. C. *Org. Prep. Proced. Int.* **2000**, *32*, 103.

(5) (a) Brighty, K. E.; Castaldi, M. J. *Synlett* **1996**, 1097. (b) Braish, T. F.; Castaldi, M.; Chan, S.; Fox, D. E.; Keltonic, T.; McGarry, J.; Hawkins, J. M.; Norris, T.; Rose, P. R.; Sieser, J. E.; Sitter, B. J.; Watson, H., Jr. *Synlett* **1996**, 1100.

(6) (a) House, H. O.; Blankley, C. J. *J. Org. Chem.* **1968**, *33*, 53. (b) Hudlicky, T.; Reddy, D. B.; Govindan, S. V.; Kulp, T.; Still, B.; Sheth, J. P. *J. Org. Chem.* **1983**, *48*, 3422. (c) Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763.

(7) (a) Blankley, C. J.; Sauter, F. J.; House, H. O. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 258; (b) Corey, E. J.; Myers, A. G. *Tetrahedron Lett.* **1984**, 3559.

(8) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805.

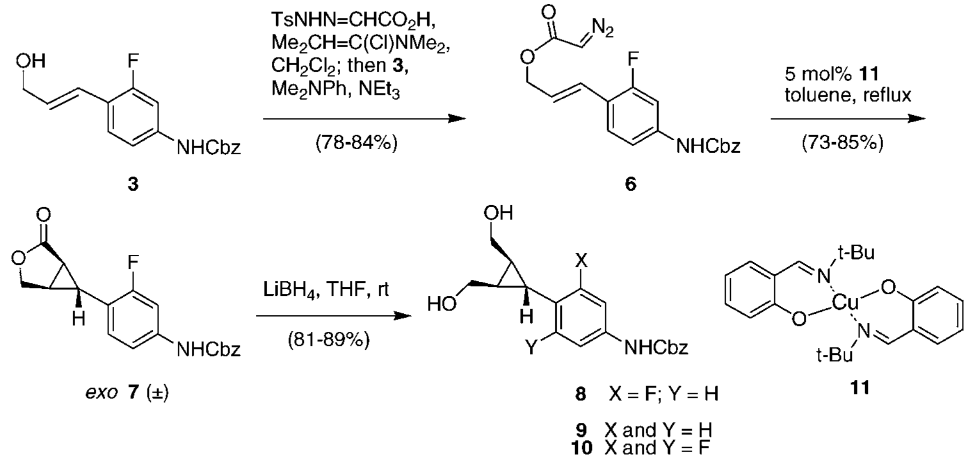
(9) (a) Devos, A.; Frisque-Hesbain, A.-M.; Colens, A.; Ghosez, L. *J. Chem. Soc., Chem. Commun.* **1979**, 1180. (b) Haveaux, B.; Dekoker, A.; Rens, M.; Sidani, A. R.; Toye, J.; Ghosez, L. *Org. Synth.* **1980**, *59*, 26.

(10) (a) Charles, R. G. *J. Org. Chem.* **1957**, *22*, 677. (b) Sacconi, L.; Ciampolini, M. *J. Chem. Soc.* **1964**, 276.

(11) ^{1}H and ^{13}C NMR spectra of **7** were compared to those reported for analogous phenyl-substituted bicyclic lactones (ref 6c and references cited therein) and were consistent with formation of the expected *exo* diastereomer.

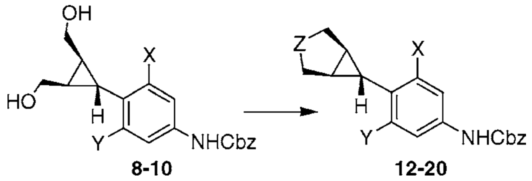
(12) This general cyclization approach has been described previously; see: Krow, G.; Hill, R. K. *Chem. Commun.* **1968**, 430.

Scheme 2. Synthesis of Key Diol Intermediates **8**−**10**



Next, we examined the synthesis of azabicyclic heterocycles **15**−**17** from diols **8**−**10**. The choice of amine nucleophile was important because eventual functionalization of the bicyclic ring nitrogen atom would be required. Less than satisfactory results were obtained using ammonia as the nucleophile,[13] and so primary amines were examined next. 4-Methoxybenzylamine was selected for initial studies since the expected tertiary bicyclic amine products would be subject to debenzylation under various conditions. Gratifyingly, reaction of the bis-mesylate with *neat* 4-methoxybenzylamine provided excellent yields of the desired bicyclic products **15**−**17** without competing oligomerization (Table 1). The use of solvent-free conditions permits reaction at ambient temperatures and without the need for strong bases, important considerations given the reactive nature of the bis-mesylate intermediates. As in reactions of sodium sulfide, the reaction with amine proceeds in good yields irrespective of substitution on the aromatic ring and is likely to be generally applicable. In subsequent work with these systems, we found that the 4-methoxybenzyl group could be readily removed via hydrogenolysis or by the action of 1-chloroethyl chloroformate[14] (for experimental details, see Supporting Information).[15]

Table 1. Synthesis of Bicyclic Heterocyles from Diols **8**−**10**



diol	X	Y	conditions[a]	product	Z	% yield
9	H	H	a, b	**12**	S	79
8	F	H	a, b	**13**	S	88
10	F	F	a, b	**14**	S	86
9	H	H	a, c	**15**	N-R	63
8	F	H	a, c	**16**	N-R	92
10	F	F	a, c	**17**	N-R	87
9	H	H	d	**18**	O	37
8	F	H	d	**19**	O	43
10[b]	F	F	d	**20**[b]	O	47

[a] Conditions: (a) Ms_2O, Et_3N, CH_2Cl_2. (b) Na_2S, DMSO. (c) NH_2R (R = 4-(MeO)PhCH$_2$), rt. (d) ^{n}BuLi (2 equiv), THF, 1.2 equiv of MsCl, −78 °C; then 1.2 equiv of ^{n}BuLi. [b] Aniline nitrogen protected as isopropyl carbamate.

For the preparation of oxabicyclic heterocycles, an alternate approach was required. We were encouraged by various reports in the literature of the spontaneous cyclization of 1,4-diols upon attempted conversion to 1,4-dihalides.[16] However, when **8** was subjected to similar conditions (e.g., PPh_3, CCl_4), only the dihalide was formed in significant quantities. We next examined literature conditions for the dehydrative cyclization of diols under strongly acidic conditions or at high temperatures in polar aprotic solvents. Unfortunately, these harsh conditions were incompatible with the benzylic cyclopropane function of **8**−**10**, and only ring-opened elimination products were isolated.

After some experimentation, a viable route to the desired oxabicyclic analogues was identified. This involved initial formation of the dianion of **8**−**10** at low temperature, followed by reaction with a slight excess of methanesulfonyl chloride. The putative monomesylate intermediate then undergoes cyclization upon treatment with additional base, thus providing the desired oxabicyclic products (**18**−**20**, Table 1). Using this process, isolated yields approaching 50% were obtainable. Further optimization of this cyclization is

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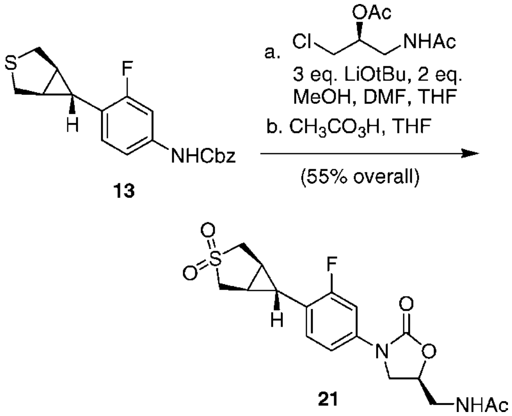
(13) Reaction of the bis-mesylate with excess aqueous ammonium hydroxide in methanol-THF provided the desired amine along with multiple side products that were not characterized.

(14) (a) Olofson, R. A.; Martz, J. T.; Senet, J.-P., Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081. (b) Yang, B. V.; O'Rourke, D.; Li, J. *Synlett* **1993**, 195.

(15) An initial attempt to oxidatively cleave the PMB group in an advanced intermediate (4.0 equiv of CAN in acetonitrile−water) produced a complex reaction mixture. This approach was not investigated further.

(16) Terunuma, D.; Kumano, K.; Motoyama, Y. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2763.

Scheme 3. Synthesis of Oxazolidinone Analogue **21**



certainly possible, although the current protocol proved to be adequate for our purposes.

The thia-, aza-, and oxabicyclic intermediates **12**−**20** could be readily converted into antibacterial oxazolidinone analogues using established protocols. The example provided in Scheme 3 is illustrative. Reaction of thiabicyclic intermediate **13** with lithium *t*-butoxide and (*S*)-acetic acid 2-acetylamino-1-chloromethyl-ethyl ester serves to install the oxazolidinone pharmacophore in a single step.[17] Oxidation of the sulfide to sulfone with peracetic acid then provides the desired oxazolidinone analogue **21**. This compound was tested against a panel of Gram positive and Gram negative bacteria and displayed antibacterial activity[18] equivalent or slightly superior to that of analogous unconstrained tetrahydrothiopyran analogues. Hence, the constrained thiabicyclo[3.1.0]hexane ring is a valid bioisostere for the monocyclic tetrahydrothiopyran ring in oxazolidinone antibacterials. A full account of the biological activities of these constrained bicyclic oxazolidinone analogues will be reported elsewhere in due course.

In conclusion, an efficient and stereospecific route to thia-, oxa-, and azabicyclo[3.1.0]hexane heterocycles has been developed. The key diol intermediates **8**−**10** are prepared in three efficient steps from substituted cinnamyl alcohols and may be rapidly converted into various heterobicyclic compounds. These bicyclic rings may find application as conformationally constrained bioisosteres of more common six-membered ring heterocycles.

Acknowledgment. We thank Marcela Gomez for performing the antimicrobial testing of compound **21** and Drs. J. V. N. Vara Prasad and Hollis Showalter for reviewing the manuscript.

Supporting Information Available: Representative synthetic procedures and spectral data (^{1}H and ^{13}C NMR, ESI-MS) for compounds **2**−**8**, **13**, **16**, **19**, and **21** and copies of the ^{1}H NMR spectra for compounds **3**−**10**, **13**, **16**, **19**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) (a) Perrault, W. R.; Pearlman, B. A.; Godrej, D. B. Process to Prepare Oxazolidinones. U.S. Patent Application Publication U.S. 2002/0169312. (b) Perrault, W. R.; Pearlman, B. A.; Godrej, D. B.; Jeganathan, A.; Yamagata, K.; Chen, J. J.; Lu, C. V.; Herrinton, P. M.; Gadwood, R. C.; Chan, L.; Lyster, M. A.; Maloney, M. T.; Moeslein, J. A.; Greene, M. L.; Barbachyn, M. R. *Org. Process Res. Dev.* **2003**, *7*, 533−546.

(18) MICs for compound **21** were ≤ 4 mg/L against a panel of *Staphylococcus. aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* strains.