Carbon−Carbon Bond Formation from Small- and Medium-Ring Lactol Acetates via Radical and Oxonium Ion Intermediates. Synthesis of (±)-Laurenan

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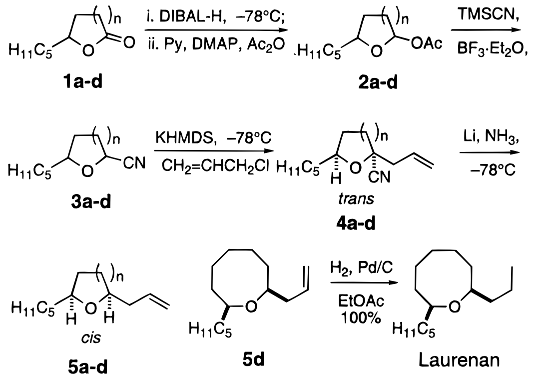
The alkylation and reductive decyanation of cyanohydrin acetonides is an efficient and stereoselective method to form new carbon−carbon bonds for the convergent synthesis of polyol chains.[1] This method, which introduces a new carbon−carbon bond adjacent to an oxygen atom in a six-membered ring, complements the wide variety of processes used to prepare C-glycosides from pyranohexoses.[2,3] Anions, radicals, cations, and carbene intermediates have all been used to prepare C-glycosides.[3,4] Described herein is an extension of the cyanohydrin coupling strategy and a complementary oxonium-ion coupling to monooxygenated five-, six-, seven-, and eight-membered rings.

The reactions of cationic, radical, and anionic intermediates at the 2-position of tetrahydropyrans usually show good stereoselectivity. The chair conformation of the six-membered ring constrains the carbon−oxygen bond to a staggered orientation in the ground state and results in significant anisotropy of reactive intermediates at the anomeric center.[5] In the cyanohydrin coupling strategy, the relative configuration of the product is determined by the preferred conformation of the intermediate anomeric radical.[6] Can the same principle be applied to other ring sizes? Selectivity in five-membered rings appears unlikely,[7] but seven-membered[8] and eight-membered[9] rings are more promising. The results are described below.

Synthesis of each cyclic cyanohydrin began with the corresponding lactone **1a**−**d**, Scheme 1.[10] Our recently reported DIBAL-H reduction and *in situ* acetylation transformed each lactone into the corresponding acetylated lactol.[11] Seven- and eight-membered hemiacetals are unstable with respect to the corresponding hydroxy aldehydes, and only by using *in situ* acetylations could the lactol acetates **2c** and **2d** be prepared. The lactol acetates were converted into cyclic cyanohydrins **3a**−**d** by treatment with TMSCN and $BF_3{\cdot}OEt_2$ at −78 °C in CH_2Cl_2.[12] Each cyanohydrin was generated and used as a mixture of diastereomers.

Scheme 1



Entry	Ring Size	Yield **2**[a]	Yield **3**[b]	Yield **4** (trans/cis)	Yield **5** (cis/trans)
a	5	93	98	36 (2.7:1)	80 (1:1)
b	6	97	89	82 (>20:1)	95 (>20:1)
c	7	65	93	82 (4.5:1)	93 (1.1:1)
d	8	95	85	74 (20:1)	89 (11.5:1)

[a] Except for **2a** all lactol acetates isolated were cis isomers (>10:1).
[b] Only **3d** was isolated as the trans isomer (>10:1), **3a-c** were produced as mixtures.

The cyclic cyanohydrins were deprotonated with KHMDS and alkylated with allyl chloride to give the allyl cyanohydrins **4a**−**d**. Alkylation of the six-, seven-, and eight-membered rings gave good yields, but the five-membered ring gave reproducibly poor yields. Both the six- and eight-membered cyanohydrins **4b** and **4d** were generated almost entirely as the *trans*-diastereomers. In each case reductive decyanation with lithium in ammonia proceeded in good yield, but the selectivity varied from >20:1 in the case of the six-membered ring **4b** to completely unselective in the case of the five-membered ring **4a**. The eight-membered ring **4d** gave a 11.5:1 mixture, but the seven-membered ring **4c** gave only a 1.1:1 mixture. The cis products predominated in both the six- and eight-membered products, **5b** and **5d**.[13] The relative configuration of the eight-membered ring product was confirmed upon hydrogenation to produce the natural product (±)-laurenan.[14] Unsaturated seven-membered ring **8** was expected to adopt a chair like conformation due to the eclipsed geometry of the double bond. Alkylation of cyclic cyanohydrin **7**[15] with allyl chloride gave a mixture of allylated cyanohydrins **8**[16] that was reduced by treatment with Li/NH_3 to give the reduced product as a 3.2:1 mixture of the two different diaster-

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[1] (a) Rychnovsky, S. D.; Zeller, S.; Skalitzky, D. J.; Griesgraber, G. *J. Org. Chem.* **1990**, *55*, 5550−5551. (b) Rychnovsky, S. D.; Griesgraber, G. *J. Org. Chem.* **1992**, *57*, 1559−1563. (c) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021−2040.

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[4] Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon Press: Exeter, 1995.

[5] (a) Malatesta, V.; McKelvey, R. D.; Babcock, B. W.; Ingold, K. U. *J. Org. Chem.* **1979**, *44*, 1872−1873. (b) Gregory, A. R.; Malatesta, V. *J. Org. Chem.* **1980**, *45*, 122−125.

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[7] See the transformation of compound **38** to **37** in: Ireland, R. E.; Norbeck, D. W.; Mandel, G. *J. Am. Chem. Soc.* **1985**, *107*, 3285−94.

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[10] Lactones **1c** and **1d** were prepared by alkylation of the *N*,*N*-dimethyl hydrazone of either cyclohexanone or cycloheptanone with 1-iodopentane, followed by hydrolysis and Baeyer−Villager oxidation (*m*-CPBA). (See the supporting information and ref 13a.)

[11] Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.*, in press.

[12] (a) Heras, F. G.; Resa−Fernández, P. *J. Chem. Soc., Perkin Trans. 1* **1982**, 903−907. (b) Utimoto, K.; Wakabayashi, Y.; Horiie, T.; Inoue, M., Shishiyama, Y.; Obayashi, M.; Nozaki, H. *Tetrahedron* **1983**, *39*, 967−973.

[13] Basis of assignment: NOE's and literature ^{13}C-NMR correlation. (a) Carling, R. W.; Clark, S. J.; Holmes, A. B. *J. Chem. Soc., Perkin Trans. 1* **1992**, 83−94. (b) Kotsuki, H. *Synlett* **1992**, 97−106.

[14] Carling R. W.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1986**, 565−567 and ref 13a.

[15] Cyclic cyanohydrin **7** was prepared by the same procedure outlined in Scheme 1. The synthesis is presented in the supporting information.

[16] Cyanohydrins **8** were isolated as a 3.6:1 mixture, but the configurations were not determined.

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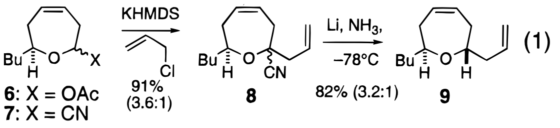
eomers. Surprisingly, the configuration of the major product was trans rather than cis.[9,13] Alkylation and reductive decyanation provides a simple strategy to append carbon chains adjacent to oxygen in six- and eight-membered rings.



Six- and eight-membered ring cyanohydrins are alkylated and reduced stereoselectively, whereas the five- and seven-membered rings show poor selectivity for both steps. One possible interpretation, that each epimeric cyanohydrin is reduced stereoselectively to one of the two epimeric products, is incorrect. Reduction of the individual seven-membered ring cyanohydrin epimers *trans*-**4c** and *cis*-**4c**[17] gave a virtually identical mixture of *cis*- and *trans*-oxepane (eq 2). Apparently, the same stereoelectronic factors that control the outcome of the alkylation reaction in six- and eight-membered rings exert a complementary effect in the reductive decyanation reaction.

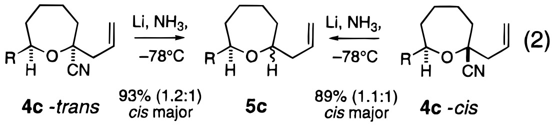
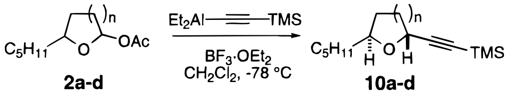


Table 1. $BF_3 \cdot OEt_2$-Catalyzed Reaction of Lactol Acetates 2a−d with Diethyl(trimethylsilyl)ethynyl)aluminum



lactol acetate	ring size	yield (%)	ratio trans/cis
2a	5	97	2:1
2b	6	93	>20:1
2c	7	95	16:1
2d	8	97	>20:1

Lactol acetates couple efficiently with carbon nucleophiles via the intermediate oxonium ion intermediates. As described in Table 1, lactol acetates **2a**−**d** reacted with diethyl((trimethylsilyl)ethynyl)aluminum under the influence of $BF_3 \cdot OEt_2$ to give alkyne products **10a**−**d** in excellent yields and with high stereoselectivities. The five-membered lactol acetate **2a** gave only a 1:2 mixture, but all of the remaining substrates gave the trans product with >16:1 selectivity. Compound **2c** could be allylated (allyl trimethylsilane, $BF_3 \cdot Et_2O$, MeCN, −40 °C, 1 h) in 92% yield to give the trans product. Reaction of **6** with diethyl((trimethylsilyl)ethynyl)aluminum also gave the expected trans product (15:1) in 91% yield. The stereoselectivity is what one would expect on the basis of the mechanistically related reductive cyclization of hydroxy ketones to oxepanes.[18] Thus, the generation and trapping of the cyclic oxonium ions with carbon nucleophiles provides an easy access to the trans product with good selectivity in 6−8-membered rings.

The two routes to α,ω-disubstituted cyclic ethers both begin with lactol acetates **2a**−**d** and have complementary stereochemical outcomes. The cyanohydrin route leads to *cis*-substituted products for six- and eight-membered rings, whereas the oxonium-ion route leads to *trans*-substituted products for the six-, seven-, and eight-membered rings. The concise synthesis of (±)-laurenan illustrates the potential of these convergent coupling reactions in medium-ring ether synthesis.

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Supporting Information Available: Sample experimental procedures and spectroscopic data are included for compounds **1**−**10** (12 pages).

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(17) Compound **4c** was separated by MPLC (SiO_2) using CH_2Cl_2 (16%), hexanes (83%), and *tert*-butyl methyl ether (1%) as the eluent.

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