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A Stereoselective Cyclization to Carbafuranose Derivatives Starting from 1,4-Bis-epoxides

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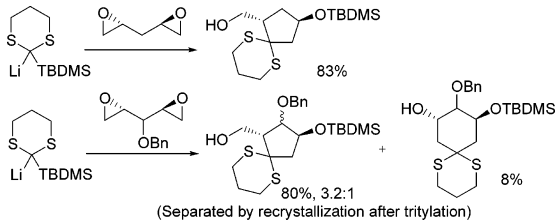
ABSTRACT



A concise synthesis of highly functionalized cyclopentane derivatives via a Brook rearrangement mediated stereoselective linchpin cyclization reaction involving *tert*-butyldimethylsilyl-1,3-dithianyllithium and homochiral 1,4-bis-epoxides is described.

Nucleosides are a pharmacologically important class of compounds, with many examples currently in clinical use.[1] Carbocyclic nucleosides have been the subject of intense research.[2] Successful examples of such nucleosides include abacavir (Figure 1),[1,3] approved as an anti-HIV drug, and

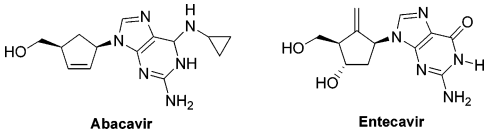


Figure 1. Examples of carbanucleosides.

entecavir,[1,4] which is currently undergoing phase III clinical trials for the treatment of chronic hepatitis B virus infections. In addition, antimalarial activity has been reported for certain carbanucleoside analogues.[5]

Many approaches have been reported for the synthesis of carbafuranose sugars as precursors for carbanucleosides,[2] and as the synthesis of novel antiviral drugs is of prime importance,[6] there is a continuing interest for new synthetic methodologies to access carbanucleosides in enantiomerically pure form, ideally with both enantiomers equally accessible.

We wish to report a very short synthesis of highly functionalized enantiopure cyclopentane derivatives **3** (Scheme 1), which would be suitable precursors for 6′-substituted

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(1) De Clercq, E. *J. Clin. Virol.* **2004**, *30*, 115.

(2) (a) Amblard, F.; Nolan, S. P.; Agrofolio, L. A. *Tetrahedron* **2005**, *61*, 7067. (b) Rodriguez, J. B.; Comin, M. J. *Mini Rev. Med. Chem.* **2003**, *3*, 95. (c) Agrofolio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev.* **2003**, *103*, 1875. (d) Schneller, S. W. *Curr. Top. Med. Chem.* **2002**, *2*, 1807. (e) Ferrero, M.; Gotor, V. *Chem. Rev.* **2000**, *100*, 4319. (f) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229. (g) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571.

(3) Hervey, P. S.; Perry, C. M. *Drugs* **2000**, *60*, 447.

(4) Levine, S.; Hernandez, D.; Yamanaka, G.; Zhang, S.; Rose, R.; Weinheimer, S.; Colonno, R. J. *Antimicrob. Agents Chemother.* **2002**, *46*, 2525.

(5) Shuto, S.; Minakawa, N.; Niizuma, S.; Kim, H.-S.; Wataya, Y,; Matsuda, A. *J. Med. Chem.* **2002**, *45*, 748.

(6) (a) El Kouni, M. H. *Curr. Pharm. Design* **2002**, ***8***, 581. (b) Richman, D. D. *Nature* **2001**, *410*, 995. (c) Wang, J.; Jin, Y.; Rapp, K. L.; Bennett, M.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **2005**, *48*, 3736.

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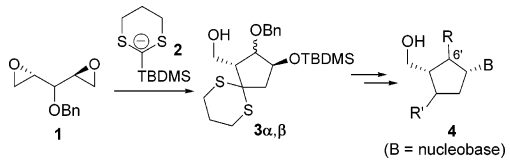
carbanucleoside analogues **4**,[7] via a stereoselective linchpin cyclization reaction involving bis-epoxide **1** and dithianyllithium **2**. Bis-epoxide **1** is derived from arabitol in two operations,[8] and as the arabitol enantiomers are available at similar cost, both D- and L-carbanucleoside derivatives would be easily accessible.

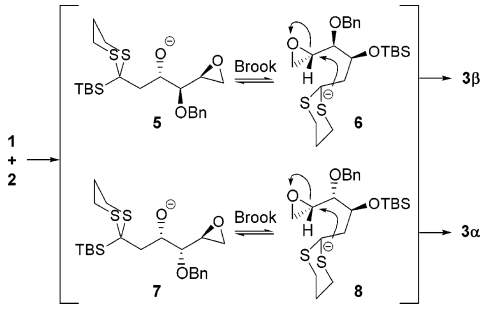
Scheme 1. Synthesis Outline



The reaction of dithianyl anion with chiral epoxide electrophiles enables the construction of partially protected aldol linkages in a stereospecific manner.[9] Fully protected aldol linkages can be directly obtained by utilizing silylated dithiane nucleophiles via a Brook rearrangement.[10] The rearrangement regenerates a dithianyl anion, which enables subsequent transformations (see below).[11] Judicious control over the timing of the Brook rearrangement[12] fully established dithiane-based "linchpin" one-pot, multicomponent coupling strategies for the construction of complex targets.[13] This process has also been investigated with mannitol-derived 1,5-bis-epoxides[14] to afford cyclohexane and cycloheptane derivatives.

With 3-benzyl-1,2:4,5-dianhydroarabitol **1**, it was envisioned that the linchpin cyclization process would proceed following the accepted mechanism as shown in Scheme 2. Ring opening of one of the diastereotopic epoxide groups by **2** would lead to a diastereoisomeric mixture of alkoxides **5**/**7**. HMPA-promoted Brook rearrangement to give **6**/**8**

Scheme 2. Mechanism of the Carbacyclization



would then be followed by 5-*exo* or 6-*exo* (7-*endo*)[15] cyclization. Literature precedence for carbanionic cyclization to δ-terminal epoxides suggest that the regioselectivity is dependent on the metal ion, with lithiated species favoring 5-*exo* ring closure.[16] Hence, the desired diastereomers **3**α and **3**β were expected as main reaction products.

In the event, we were delighted to observe that reaction of **2**, obtained by *tert*-BuLi-mediated deprotonation of 2-*tert*-butyldimethylsilyl-1,3-dithiane **9**, with **1** proceeded as depicted above with high 5-*exo* selectivity (Table 1). The double-addition product **11** was only formed in very small amounts in all cases. As expected, a mixture of cyclopentane diastereoisomers was formed, and **3**β proved to be the major diastereoisomer (see below).

Varying the temperature (entries 1−4) revealed −45 to −18 °C to be the optimum temperature range for the yield of **3** (entries 2−3). With increasing temperature, a decrease in the diastereoselectivity **3**β/**3**α was observed as well as an increase in the formation of the six-membered cyclization product **10**.

Decreasing the concentration to 0.05 M led to an increased yield of **3** (entry 5 vs 2). Reducing the concentration further led to decreased yields of **3**, but a greater amount of **1** was recovered (entries 6 and 7). Replacing THF with Et_2O as solvent led to almost identical yields of **3**, but an increased selectivity toward **3**β was observed (entry 8 vs 2). The efficiency of carbacyclization was found to be significantly hampered when the HMPA/THF ratio was reduced to 1:30 (entry 9).

When conducting the cyclization at −30 °C, a higher yield was observed (entry 10 vs 7). In the end, addition of molecular sieves led to a dramatic rise in the cyclization yields (entries 11 vs 10, 12 vs 7). Increasing the HMPA/THF ratio to 1:9 furnished a 77% yield of **3** (entry 13), and the use of a slight excess of **2** completed the optimization in which **3**β and **3**α were obtained in 80% combined yield (3.2:1), together with 8% of **10** (entry 14). Increasing the concentration further to 0.05 M did not lead to improved results (entry 15).

(7) Synthesis of 6′-substituted nucleosides: (a) Yang, Y.-Y.; Meng, W.-D.; Qing, F.-L. *Org. Lett.* **2004**, *6*, 4257. (b) Hong, J. H.; Oh, C.-H.; Cho, J.-H. *Tetrahedron* **2003**, *59*, 6103. (c) Bianco, A.; Celletti, L.; Mazzei, R. A.; Umani, F. *Eur. J. Org. Chem.* **2001**, 1331. (d) Wachtmeister, J.; Classon, B.; Samuelsson, B.; Kvarnström, I. *Tetrahedron* **1997**, *53*, 1861. (e) Bisacchi, G. S.; Chao, S. T.; Bachard, C.; Daris, J. P.; Innaimo, S.; Jacobs, G. A.; Kocy, O.; Lapointe, P.; Martel, A.; Merchant, Z.; Slusarchyk, W. A.; Sundeen, J. E.; Young, M. G.; Colonno, R.; Zahler, R. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 127. (f) Tanaka, M.; Norimine, Y.; Fujita, T.; Suemune, H.; Sakai, K. *J. Org. Chem.* **1996**, *61*, 6952. (g) Altmann, K.-H.; Kesselring, R.; Pieles, U. *Tetrahedron* **1996**, *52*, 12699. (h) Katagiri, N.; Nomura, M.; Sato, H.; Kaneko, C.; Yusa, K.; Tsuruo, T. *J. Med. Chem.* **1992**, *35*, 1882.

(8) (a) Dreyer, G. B.; Boehm, J. C.; Chenera, B.; DesJarlais, R. L.; Hassell, A. M.; Meek, T. D.; Tomaszek, T. A., Jr.; Lewis, M. *Biochemistry* **1993**, *32*, 937. (b) Schreiber, S. L.; Sammakia, T.; Uehling, D. E. *J. Org. Chem.* **1989**, *54*, 15. (c) Leung, L. M. H.; Gibson, V.; Linclau, B. *Tetrahedron: Asymmetry* **2005**, *16*, 2449.

(9) Yus, M.; Nájera, C.; Foubelo, F. *Tetrahedron* **2003**, *59*, 6147.

(10) (a) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065. (b) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77.

(11) (a) Shinokubo, H.; Miura, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1993**, *34*, 1951. (b) Tietze, L. F.; Geissler, H.; Gewert, J. A.; Jakobi, U. *Synlett* **1994**, 511. (c) Fischer, M.-R.; Kirschning, A.; Michel, T.; Schaumann, E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 217.

(12) Smith, A. B., III; Boldi, A. M. *J. Am. Chem. Soc.* **1997**, *119*, 6925

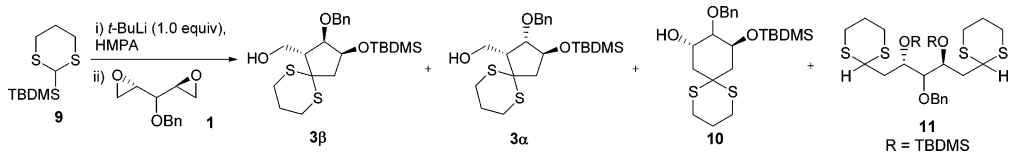
(13) (a) Smith, A. B., III; Pitram, S. M.; Boldi, A. M.; Gaunt, M. J.; Sfouggatakis, C.; Moser, W. H. *J. Am. Chem. Soc.* **2003**, *125*, 14435. (b) Smith, A. B., III; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365.

(14) (a) Le Merrer, Y.; Gravier-Pelletier, C.; Maton, W.; Numa, M.; Depezay, J.-C. *Synlett* **1999**, 1322. (b) Bräuer, N.; Dreessen, S.; Schaumann, E. *Tetrahedron Lett.* **1999**, *40*, 2921.

(15) For nomenclature, see: Narayan, R. S.; Sivakumar, M.; Bouhlel, E.; Borhan, B. *Org. Lett.* **2001**, *3*, 2489 and references therein.

(16) (a) Babler, J. H.; Bauta, W. E. *Tetrahedron Lett.* **1984**, *25*, 4323. (b) Cooke, M. P., Jr.; Houpis, I. N. *Tetrahedron Lett.* **1985**, *26*, 3643. (c) Rieke, R. D.; Wehmeyer, R. M.; Wu, T.-C.; Ebert, G. W. *Tetrahedron* **1989**, *45*, 443. (d) Fleming, I.; Martínez de Marigorta, E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 889.

Table 1. Optimization of the Linchpin Cyclization Process



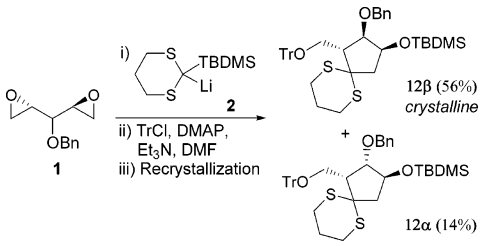
entry	**9** (equiv)	concn (M)	HMPA/THF	*T* (°C)	time (min)	mol sieve	yield of **3**β[a] (%)	yield of **3**α[a] (%)	combined yield of **3** (%)	ratio **3**β/**3**α	yield of **10**[b] (%)	unreacted **1**[b] (%)
1	1.1	0.1	1:10	−75	300		37	7	44	5.3:1	1	23
2	1.0	0.1	1:10	−45	30		43	13	56	3.3:1	4	7
3	1.0	0.1	1:10	−18	15		44	17	61	2.6:1	4	0
4	1.0	0.1	1:10	0	10		33	18	51	1.8:1	7	0
5	1.0	0.05	1:10	−45	40		49	12	61	4.1:1	4	13
6	1.1	0.033	1:10	−45	180		44	9	53	4.9:1	3	24
7	1.1	0.03	1:10	−45	180		44	9	53	4.9:1	1	17
8	1.1	0.03	1:10[c]	−45	120		47	8	55	5.9:1	3	2
9	1.1	0.03	1:30	−45	120		27	12	39	2.3:1	4	0
10	1.1	0.03	1:10	−30	100		50	14	64	3.6:1	5	0
11	1.1	0.03	1:10	−30	75	x	59	17	76	3.5:1	6	0
12	1.1	0.03	1:10	−45	120	x	54	15	69	3.6:1	6	0
13	1.1	0.03	1:9	−30	75	x	62	15	77	4.1:1	4	0
14	1.3[d]	0.03	1:9	−30	90	x	61	19	80	3.2:1	8[e]	0
15	1.3[d]	0.05	1:9	−30	90	x	55	19	76	2.9:1	7[e]	0

[a] Isolated yields after separation by HPLC. [b] Compounds **10** and **1** were inseparable, and their ratio was estimated from the corresponding ^{1}H NMR spectra. The ratios and relative stereochemistry of **10**α/**10**β could not be determined. [c] Et_2O instead of THF. [d] 1.3 equiv of *t*-BuLi used. [e] Isolated yield.

Interestingly, **10** was isolated almost as a single diastereoisomer, but we were unable to establish the relative stereochemistry of the major isomer.

The **3**α/β diastereoisomers were only separable by tedious preparative HPLC, which is clearly unsatisfactory from a practical preparative point of view. In the event, we were delighted to find that after tritylation (Scheme 3), the highly

Scheme 3. Separation of the Diastereoisomers after Tritylation



crystalline derivative **12**β could be easily separated from the corresponding α-isomer by recrystallization from hot ethanol, affording 51% yield from bis-epoxide **1**. Single X-ray crystallographic analysis confirmed the relative stereochemistry on the cyclopentane ring (Figure 2). Purification of the remaining filtrate by HPLC afforded pure minor diastereomer **12**α in 14% yield, with an additional 5% of **12**β.

The recrystallization process greatly facilitated the purification procedure on a large scale.

The cyclization was further investigated by a set of control experiments (Scheme 4). Though the two diastereotopic epoxide moieties of the *pseudo*-C_2-symmetric bis-epoxide **1** are expected to react at different rates, the obtained β/α ratio of **3** appeared relatively large. However, epoxide opening of **1** by **2** in the absence of HMPA in Et_2O led to the adducts **13** and **14** in a 2:1 ratio (NMR), which unambiguously proved that the diastereotopic epoxide groups reacted at significantly different rates. The ratio observed here was smaller than the ratio obtained in the linchpin cyclization process, but this could be due to the absence of HMPA. Reaction of nonsilylated dithianyl anion **16** with **1** in the presence of the usual amount of HMPA (in THF) did lead to a 2.4:1 diastereoselectivity for the epoxide opening (**18**/**19**), despite the significantly reduced size of the nucleophile.

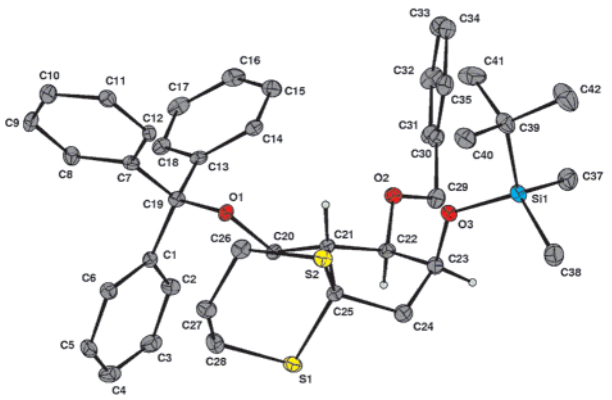
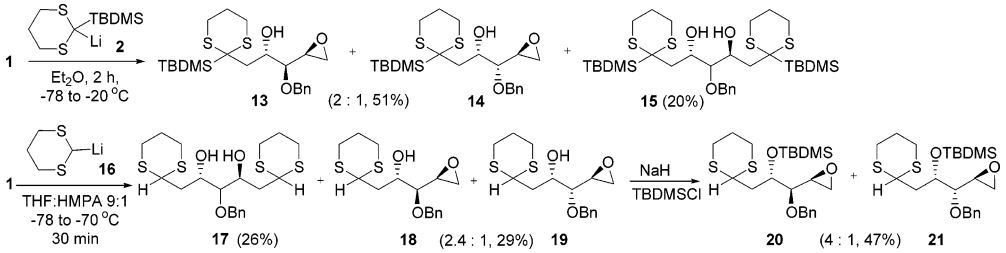


Figure 2. ORTEP representation of the crystal structure of **12**β.

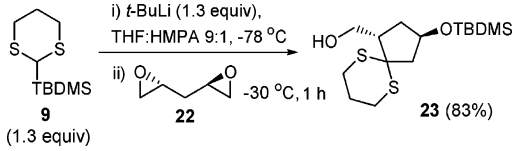
Scheme 4. Investigation of the Diastereoselectivity by Preventing the Brook Rearrangement



Under the conditions as shown in Scheme 4, when the cyclization process is not possible, a relatively large amount of the diaddition products **15** and **17** was formed despite the use of only 1 equiv of **2**. In contrast, only very small amounts of the diaddition product **11** have been isolated from the cyclization experiments (Table 1), with no **11** detected at all under the optimized conditions (entry 15). This confirms that the HMPA-mediated Brook rearrangement is a very fast process[12] and that in the concentration range investigated, the actual 5-*exo* (and 6-*exo*) cyclization reaction is much faster than the epoxide opening by **2**. In addition, the absence of **20** and **21**, which were independently synthesized from **18**/**19** (Scheme 4), in the optimization experiments (Table 1) further suggests that the cyclization is a facile process and that the **3***β*/**3**α ratio relates to the epoxide opening and not to an incomplete cyclization of **8**.

Finally, the optimum conditions for the linchpin cyclization were applied with (2*S*,4*S*)-1,2:4,5-diepoxypentane **22** as substrate, which is also available in both enantiomeric forms at similar cost,[17] with the resulting carbocycle **23** obtained in equally excellent yield (Scheme 5). Interestingly, no 6-*exo* cyclization product was observed in this case.

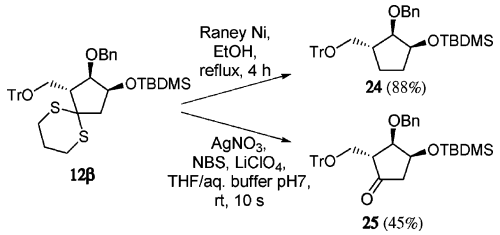
Scheme 5. Linchpin Cyclization Using Bis-epoxide **22**



The preliminary results for the further conversion of the dithianyl group are given in Scheme 6. Reduction with Raney nickel lead to the cyclopentane derivative **24** in excellent yield. For the hydrolysis to the ketone **25**, a yield of 45% has been achieved, and further optimization of this transformation is underway.

In summary, it was demonstrated that a linchpin cyclization sequence involving 1,4-bis-epoxides and dithianyllithium **2** proceeds in excellent yield with high 5-*exo* selectivity, giving access to highly substituted carbafuranose-type structures. As both enantiomers of both 1,4-bis-epoxides are available, and both diastereomers **12**α/*β* could be efficiently separated, the methodology is undoubtedly an attractive approach toward the synthesis of 6′-substituted carbanucleosides. The configuration of the OTBDMS substituent in **12**/**23** is ideally set up for subsequent nucleobase introduction. Current efforts in our laboratory are focusing on the transformation of **12**α/*β*, and of **23**, to carbanucleoside analogues.

Scheme 6. Further Conversion of the Dithianyl Group



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Supporting Information Available: Experimental procedures and spectral data, including copies of ^{1}H and ^{13}C NMR spectra, for **3**α/*β*, **10**, **11**, **12**α/*β*, and **23**−**25**, and the crystal information file (CIF) for compound **12***β*. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) (a) Rychnovsky, S. D.; Griesgraber, G.; Powers, J. P. *Org. Synth.* **2000**, *77*, 1. (b) Boydell, A. J.; Jeffery, M. J.; Bürkstümmer, E.; Linclau, B. *J. Org. Chem.* **2003**, *68*, 8252.

(18) The United Kingdom Database Service. Fletcher, D. A.; McMeeking, R. F.; Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746.