

# Enantioselective Synthesis and Selective Monofunctionalization of (4*R*,6*R*)-4,6-Dihydroxy-2,8-dioxabicyclo[3.3.0]octane

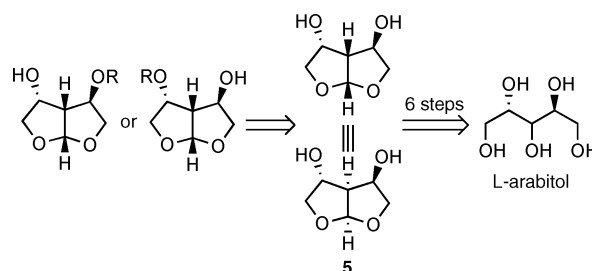
Bruno Linclau,\* Martin J. Jeffery,<sup>†</sup> Solen Josse,<sup>‡</sup> and Cyrille Tomassi

University of Southampton, School of Chemistry,  
Highfield, Southampton SO17 1BJ, U.K.

bruno.linclau@soton.ac.uk

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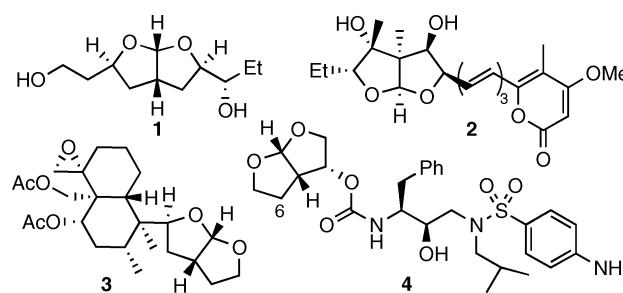
## ABSTRACT



An efficient, enantioselective synthesis of a disubstituted bis-THF scaffold **5** is described, as well as an efficient differentiation of the 1,3-diol unit.

The 2,8-dioxabicyclo[3.3.0]octane ring system (hexahydrofuro[2,3-*b*]furan, also called bistetrahydrofuran or bis-THF) is present in a limited number of natural products including communiol D **1**,<sup>1</sup> the ATPase inhibitor asteltoxin **2**,<sup>2</sup> and dihydroclerodin **3**.<sup>3</sup> The last is a member of the large clerodane family, many of which were found to have interesting biological activities, including antifeedant, antiviral, antitumor, and antibiotic activity (Figure 1).<sup>3</sup> Benzanulated bis-THF rings are found in aflatoxins,<sup>4</sup> and they have been used as a template for the development of cholinesterase inhibitors.<sup>5</sup>

A particularly successful example of a bis-THF-containing drug candidate is the nonpeptidic HIV-protease inhibitor



**Figure 1.** Examples of saturated bis-THF-containing compounds.

TMC-114 **4**,<sup>6</sup> which has recently been approved by the FDA for treatment against AIDS under the name Darunavir. This compound was reported to be very active not only against the wild-type virus but also against a series of mutant strains.<sup>7</sup>

\* Current address: Evotec (U.K.) Ltd., 114 Milton Park, Abingdon, Oxon OX14 4SD, U.K.

<sup>†</sup> Current address: Laboratoire des Glucides UMR6219, Université de Picardie Jules Verne, 33 rue Saint Leu, 80039 Amiens, France.

(1) (a) Che, Y.; Gloer, J. B.; Scott, J. A.; Malloch, D. *Tetrahedron Lett.* **2004**, 45, 6891. (b) Enomoto, M.; Nakahata, T.; Kuwahara, S. *Tetrahedron* **2006**, 62, 1102.

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(3) Reviews: (a) van Beeck, T. A.; de Groot, A. *Recl. Trav. Chim. Pays-Bas* **1986**, 105, 513. (b) Merritt, A. T.; Ley, S. V. *Nat. Prod. Rep.* **1992**, 9, 243.

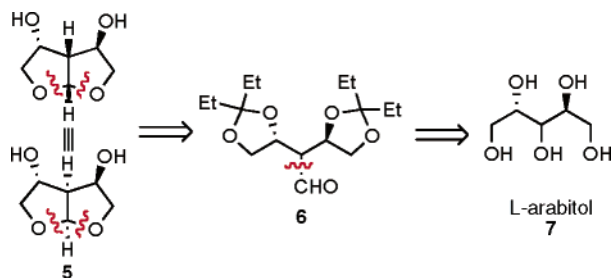
(4) Reviews: (a) Schuda, P. F. *Top. Curr. Chem.* **1980**, 91, 75. (b) Minto, R. E.; Townsend, C. A. *Chem. Rev.* **1997**, 97, 2537.

(5) Luo, W.; Yu, Q.-S.; Kulkarni, S. S.; Parrish, D. A.; Holloway, H. W.; Tweedie, D.; Shafferman, A.; Lahiri, D. K.; Brossi, A.; Greig, N. H. *J. Med. Chem.* **2006**, 49, 2174.

With its low molecular weight, high degree of rigidity, and association with biological activity, the bis-THF structure is an interesting scaffold. Any substitution on a nonfused bond position renders the bicycle chiral. There are two H-bond acceptors, which, incidentally, play a crucial role in the interaction of TMC-114 with the protease enzyme.

We were interested in the synthesis of the chiral 4,6-disubstituted bis-THF **5** (Scheme 1) as a versatile intermedi-

**Scheme 1.** Retrosynthetic Analysis



ate for scaffold applications, in particular, toward the synthesis of TMC-114 analogues with substitution at the exo-6-position, where modeling has suggested that additional interactions with the HIV-protease might be possible. To the best of our knowledge, such analogues have not yet been reported. An essential part of this work entailed the investigation toward a selective differentiation of the diastereotopic alcohols. The synthesis and monofunctionalization of **5** is reported herein.

The retrosynthetic analysis is shown in Scheme 1. Disconnections at the acetal center lead to **6**. The acid-catalyzed formation of a bis-THF ring via a central formyl group, or from a preformed five-membered (hemi)-acetal, is known.<sup>8</sup> Further disconnection as indicated leads to L-arabitol **7** as starting material. Importantly for scaffold applications, both arabitol enantiomers are commercially available at similar cost.

A key feature in this approach is that, starting from “pseudo- $C_2$ -symmetric” arabitol, the central carbon atom remains nonstereogenic throughout the sequence, thus minimizing diastereoselectivity issues. In addition, the selective formation of a cis-fused bis-THF system was expected under thermodynamic control.

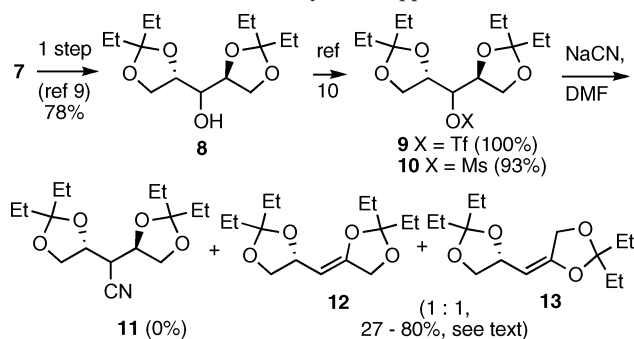
The synthesis of the aldehyde **6** was first envisaged via reduction of a cyano group.<sup>8b</sup> Hence, the nitrile **11** was

(6) (a) Ghosh, A. K.; Shin, D. W.; Swanson, L.; Krishnan, K.; Cho, H.; Hussain, K. A.; Walters, D. E.; Holland, L.; Buthod, J. *Il Farm.* **2001**, *56*, 29. (b) Ghosh, A. K.; Kincaid, J. F.; Cho, W.; Walters, D. E.; Krishnan, K.; Hussain, K. A.; Koo, Y.; Cho, H.; Rudall, C.; Holland, L.; Buthod, J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 687.

(7) Surleraux, D. L. N. G.; Tahri, A.; Verschuere, W. G.; Pille, G. M. E.; de Kock, H. A.; Jonckers, T. H. M.; Peeters, A.; De Meyer, S.; Azijn, H.; Pauwels, R.; de Bethune, M.-P.; King, N. M.; Prabu-Jeyabalan, M.; Schiffer, C. A.; Wigerinck, P. B. T. P. *J. Med. Chem.* **2005**, *48*, 1813.

(8) Selected examples toward saturated, monoacetal bis-THF via a formyl group: (a) Alonso, F.; Lorenzo, E.; Yus, M. *Tetrahedron Lett.* **1997**, *38*, 2187. (b) Vader, J.; Sengers, H.; De Groot, A. *Tetrahedron* **1989**, *45*, 2131. (c) Roggenbuck, R.; Schmidt, A.; Eilbracht, P. *Org. Lett.* **2002**, *4*, 289. Via acetal exchange: (d) Schreiber, S. L.; Satake, K. *J. Am. Chem. Soc.* **1984**, *106*, 4186. (e) Tadano, K.-I.; Yamada, H.; Idogaki, Y.; Ogawa, S.; Suami, T. *Tetrahedron Lett.* **1988**, *29*, 655.

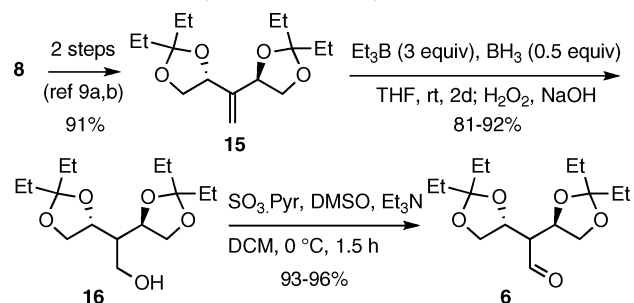
**Scheme 2.** Cyanide Approach



targeted (Scheme 2). To this end, selective protection of arabitol under kinetic conditions to the 1,2:4,5-diacetal **8**<sup>9</sup> was followed by conversion to the triflate **9** and mesylate **10** in high yield (100% and 93%).<sup>10</sup> However, reaction of **9** with NaCN in DMF at room temperature only returned elimination products **12** and **13** in 80% combined yield. The formation of the olefin isomers arises from unselective cyanide attack of the diastereotopic  $\beta$ -protons. Attempting to favor substitution over elimination by lowering the reaction temperature (0 °C; -40 °C) only reduced the yield (63%; 59%). When the mesylate **10** was subjected to NaCN, no reaction occurred at room temperature, and only 27% of **12/13** was obtained after 1 day at 110 °C.

Next, the synthesis of **6** was investigated via an alkene hydroboration/oxidation sequence.<sup>8a</sup> Oxidation of **8**<sup>9a,b</sup> and Wittig reaction led to **15**<sup>9b</sup> in excellent yield (Scheme 3).

**Scheme 3.** Synthesis of the Cyclization Precursor **6**



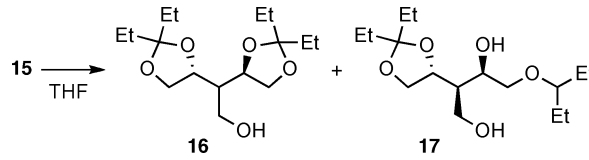
The subsequent hydroboration reaction proved to be an eventful step (see below), but by using diethylborane as reagent, a good yield of the alcohol **16** was obtained after oxidative workup. Finally, Parikh–Doering oxidation<sup>11</sup> of **16** gave **6** in excellent yield.

The hydroboration reaction was initially investigated with  $BH_3 \cdot DMS$  as reagent which led to the formation of an acetal

(9) (a) Linclau, B.; Boydell, A. J.; Clarke, P. J.; Horan, R.; Jacquet, C. *J. Org. Chem.* **2003**, *68*, 1821. (b) Maleczka, R. E., Jr.; Terrell, L. R.; Geng, F.; Ward, J. S., III. *Org. Lett.* **2002**, *4*, 2841. See also: (c) Terauchi, T.; Sato, I.; Tsukada, T.; Kanoh, N.; Nakata, M. *Tetrahedron Lett.* **2000**, *41*, 2649.

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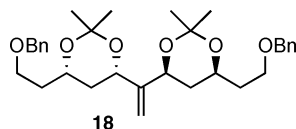
**Table 1.** Hydroboration Experiments of **15**


entry	borane (equiv)	temp (°C)	time	yield % <sup>a</sup>	
				<b>16</b>	<b>17</b> <sup>b</sup>
1	BH <sub>3</sub> ·DMS (5) <sup>c</sup>	rt	2 days	32	19
2	BH <sub>3</sub> ·DMS (5) <sup>c</sup>	50	2 days	26	41
3	BH <sub>3</sub> ·THF (5)	rt	2 days	35	0
4	BH <sub>3</sub> ·THF (10)	40	1 day	0	84
5	Et <sub>3</sub> B·THF (3.0), BH <sub>3</sub> ·THF (1.0)	rt	22 h	80	9
6	Et <sub>3</sub> B·THF (3.0), BH <sub>3</sub> ·THF (0.5)	rt	2 days	92	0

<sup>a</sup> Isolated yield. <sup>b</sup> See Supporting Information for confirmation of relative stereochemistry. <sup>c</sup> Toluene was used as solvent.

reduction byproduct **17** (entry 1, Table 1). When the reaction was executed at elevated temperature, **17** was obtained in higher yield (entry 2). Interestingly, a single diastereomer was obtained representing an efficient desymmetrization of the C<sub>2</sub>-symmetric **15**.

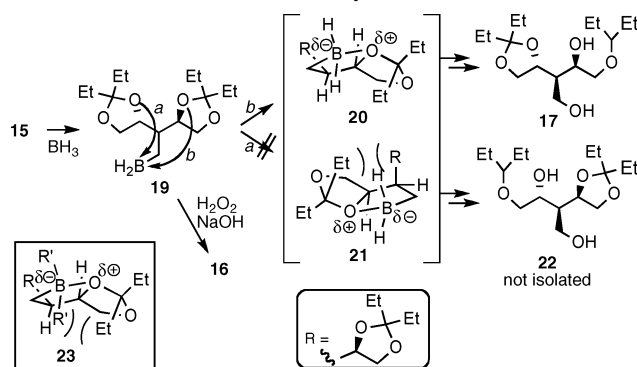
Such a desymmetrization process starting from **18** has been employed by Nakata in the synthesis of the C11–C23 segment of Swinholide A, in which the desymmetrized and hydroborated products were obtained in a 2:1 ratio.<sup>12</sup>



A rationale for the selective acetal reduction proposed by Nakata<sup>12</sup> fully explains our results, and is given in Scheme 4.

Initial hydroboration leads to **19** which, after oxidative workup, leads to the desired **16**. However, intramolecular B–O coordination initiates reductive acetal ring opening. With the homotopic acetal groups of **15** now transformed into diastereotopic groups, two possible diastereomeric intermediates **20** and **21** can be formed, in which the coordination effectively results in the formation of a [3.3.0]-bicyclooctane ring system with the substituent R in the exo position (**20**) or in the endo position (**21**). Steric factors result in the formation of **20** being the preferred pathway, explaining the observed diastereoselectivity.

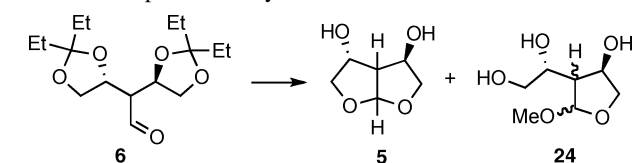
Hence, it was envisioned that preventing B–O coordination would be key in maximizing the yield of **16**. Indeed, BH<sub>3</sub>·THF in THF led to exclusive formation of **16** albeit in low yield (entry 3). However, heating the reaction mixture

**Scheme 4.** Diastereoselectivity of the Acetal Reduction

led to **17** as the only product in 84% yield (entry 4). Next, the use of dialkylboranes was investigated, as after B–O coordination (as in **23**) the endo-R' group would sterically clash with the endo-ethyl group. Unfortunately, 9-BBN did not react with **15**, but use of Et<sub>2</sub>BH, formed in situ from metathesis reaction with Et<sub>3</sub>B and BH<sub>3</sub>,<sup>13</sup> led to the desired **16** in excellent yield after oxidative workup. An excess of Et<sub>3</sub>B was necessary to completely remove BH<sub>3</sub> from the metathesis equilibrium reaction (Table 1, entries 5 and 6).

Hence, the hydroboration of the C<sub>2</sub>-symmetric alkene **15** was optimized for both reaction pathways.

Finally, the conversion of **6** to **5**, which requires alcohol deprotection followed by cyclic acetal formation, was achieved in one pot (Table 2). Reaction in MeOH/H<sub>2</sub>O (22:1

**Table 2.** Deprotection/Cyclization toward the bis-THF **5**

entry	conditions	time	yield (%) <sup>a</sup>	
			<b>5</b>	<b>24</b> <sup>b</sup>
1	CSA (15 mol %), MeOH/H <sub>2</sub> O	44 h	62	25
2	CSA (15 mol %), THF, MeOH (5 equiv), H <sub>2</sub> O (6.6 equiv)	13 days	78	0
3	DCM/TFA/H <sub>2</sub> O (100:10:1 v/v)	0.5 h	90	0

<sup>a</sup> Isolated yield. <sup>b</sup> Relative stereochemistry not determined.

v/v) with 15 mol % of CSA smoothly led to **5** in high yield on a small scale. However, on a large scale, incomplete reaction was observed (entry 1). In this case, a side product **24** was also isolated, resulting from trapping of the corresponding oxocarbenium intermediate with MeOH (relative stereochemistry not determined). When THF was introduced as the solvent, the reaction time significantly increased, with 78% of **5** isolated after 13 days. Despite no **24** being formed,

(12) Nakata, T.; Komatsu, T.; Nagasawa, K.; Yamada, H.; Takahashi, T. *Tetrahedron Lett.* **1994**, 35, 8225. With bis-*p*-methoxybenzylidene acetals instead of acetonides, the corresponding diol was obtained in 88% yield. See also: Horita, K.; Inoue, T.; Tanaka, K.; Yonemitsu, O. *Tetrahedron Lett.* **1992**, 33, 5537.

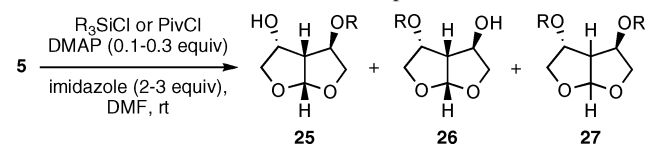
(13) Koster, R.; Binger, P. *Inorg. Synth.* **1974**, 15, 141.

the reaction time was unacceptably long. Using TFA as acid, the reaction rate was dramatically increased. Even on a large scale (44 mmol), only bis-THF **5** was isolated in 90% yield after a 30 min reaction time.

With a successful synthesis of **5** in hand, efforts were directed toward a practical differentiation of the 1,3-diol system, an essential requirement for scaffold applications. It was anticipated that the bent shape of the bicyclo[3.3.0]-octane system would enable selective monofunctionalization of the diastereotopic alcohol groups, located on the endo and the more accessible exo faces.<sup>14</sup>

Our initial results are given in Tables 3 and 4. Alcohol differentiation was fully selective with the bulky TIPSCl

**Table 3.** Exo-Selective Protection Experiments

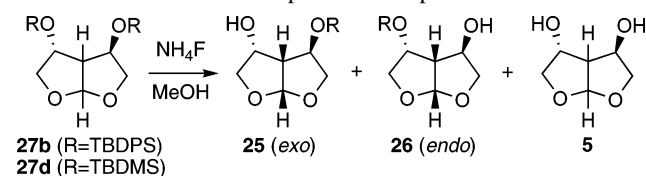


entry	reagent R-Cl (equiv)	time (h)	yield (%) <sup>a</sup>		
			25	26	27
1	<b>a</b> TIPSCl (1.5)	22	80	0	0
2	<b>b</b> TBDPS-Cl (1.5)	22.5	55	0	45
3	<b>b</b> TBDPS-Cl (1.0)	24	63	5	11
4	<b>c</b> Piv-Cl (1.1) <sup>b</sup>	25	57	0	19

<sup>a</sup> Isolated yield. <sup>b</sup> DIPEA was used instead of imidazole, and THF was used instead of DMF.

(Table 3, entry 1), with the exo-silyl ether **25a** isolated in excellent yield. Reaction with TBDPSCl was less selective (entry 2), with bis-silylated **27b** also formed. Interestingly, when using 1 equiv, a small amount of endo-product **26b**

**Table 4.** Exo-Selective Deprotection Experiments



entry	R	NH <sub>4</sub> F (equiv)	temp	time	yield (%) <sup>a</sup>			
					25	26	5	27 <sup>b</sup>
1	<b>b</b> TBDPS	8	rt	4 days	0	45	36	0
2 <sup>c</sup>	<b>b</b> TBDPS	4	reflux	2.5 h	<1	50	<5	<sup>d</sup>
3	<b>b</b> TBDPS	1.2	reflux	24 h	0	34	<1	62
4	<b>d</b> TBDMS	1.2	reflux	22 h	13	61	18	3 <sup>e</sup>

<sup>a</sup> Isolated yield. <sup>b</sup> Recovered starting material. <sup>c</sup> Starting from the crude reaction mixture after silylation. <sup>d</sup> Not determined (coeluted with excess chlorosilane). <sup>e</sup> **27d**.

was still isolated (entry 3), indicating that endo protection commenced before all exo-OH had reacted. The reaction of **5** with pivaloyl chloride (1.1 equiv) was also not completely exo selective (3:1 ratio), but no endo-product **26c** was observed (entry 4). The structure of **25b** and **26b** was proven by X-ray crystallographic analysis of the corresponding *p*-nitrophenolate derivatives (see Supporting Information).

To obtain the endo-protected scaffold, a two-step sequence was investigated in which an exo-selective deprotection was attempted starting from the bis-silyl ethers **27b** and **27d** (Table 4), which were obtained by protection of **5** with excess chlorosilane (76% resp 79%).

The use of TBAF/THF led to virtually unselective deprotection (not shown), but good selectivity was achieved with the milder NH<sub>4</sub>F/MeOH system.<sup>15</sup> Reaction at room temperature was, as expected,<sup>15</sup> sluggish, but selective exo deprotection had taken place, next to full deprotection (entry 1). Halving the amount of NH<sub>4</sub>F, while increasing the reaction temperature, led to a smaller amount of endo deprotection, with a good yield of **26b** in only 2.5 h (entry 2). Further lowering the number of NH<sub>4</sub>F equivalents while increasing the reaction time eliminated any endo deprotection, but only a low conversion was achieved (entry 3). In the event, TLC analysis is required to determine when to terminate the reaction. Interestingly, the endo deprotection was observed only when the exo-TBDPS group already had reacted. In contrast, the deprotection of the corresponding TBDMS-protected bis-THF **27d** was much less selective (entry 4).

In conclusion, an efficient, high-yielding synthesis of the interesting scaffold **5** is reported, as well as a methodology for selective differentiation of the alcohol groups. Research toward the synthesis and biological evaluation of TMC-114 analogues is underway and will be reported in due course.

**Acknowledgment.** We thank the EPSRC and NV Tibotec for financial support and Dr. Dominique Surleraux and Dr. Tim Jonckers (NV Tibotec) for helpful discussions. We wish to acknowledge the use of the EPSRC's Chemical Database Service at Daresbury.<sup>16</sup>

**Supporting Information Available:** Experimental procedures and spectral data, including copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra, for **5**, **16**, **17**, **25a**, and **26b**; stereochemical confirmation of **17**; X-ray structures of **5**; and the *p*-nitrophenolates of **25b** and **26b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(15) Zhang, W.; Robins, M. J. *Tetrahedron Lett.* **1992**, 33, 1177.

(16) Fletcher, D. A.; McMeeking, R. F.; Parkin, D. J. *Chem. Inf. Comput. Sci.* **1996**, 36, 746.