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A General Strategy for the Diastereoselective Synthesis of 2,6-Diaryl-3,7-dioxabicyclo[3.3.0]octane Lignans

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Abstract: A strategy for the stereoselective synthesis of all the possible diastereoisomers of the 2,6-diaryl-3,7-dioxabicyclo-[3.3.0]octane (furofuran) lignans from a single dihydrofuran precursor is described. The key steps involve a diastereocontrolled templated cationic cyclization followed by stereoselective reduction of the resulting methyl glycoside.

The furofurans, compounds containing the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane skeleton, represent one of the major subclasses of the lignan family of natural products.[1] Structural variation is observed through the nature of the aryl groups, which may be sited on either the *exo* or *endo* face of the bicyclic core, e.g., **1**−**4**, Figure 1. Reflecting this structural and stereochemical diversity, a wide range of biological activities has been reported for these compounds. This, in turn, has prompted considerable synthetic effort focused on the preparation of these compounds in a stereocontrolled fashion. There have been a large number of syntheses of the thermodynamically more favorable *exo-exo* substituted core[2] but relatively few selective approaches to the alternative *endo-exo*[3] and *endo-endo* substituted isomers.[4] Most of these approaches are substrate specific providing an entry to one particular stereochemical series. In this paper, we describe a divergent strategy by which all possible diastereoisomers of an unsymmetrical 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane skeleton can be generated from a common dihydrofuran intermediate.

We have previously reported that the thermal rearrangement of vinyl epoxides **5** affords *cis*-disubstituted dihydrofuryl esters **6** with high levels of stereocontrol. Following reduction to the alcohol **7**, Lewis acid catalyzed cyclization gives either the *endo-endo* **8** or *endo-exo* furofuran acetal **9** depending on the reaction temperature, Scheme 1.[5,6]

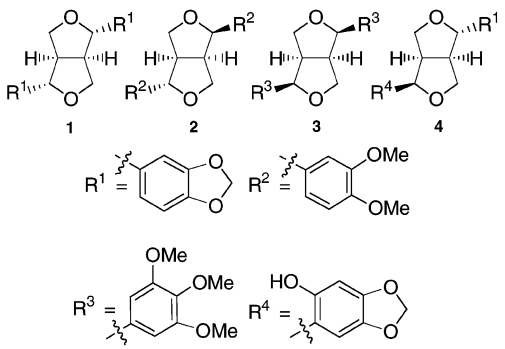

FIGURE 1. Structural variation in natural furofuran lignans (**1**, sesamin; **2**, epieudesmin; **3**, diyangambin; **4**, 2′-hydroxyasarinin).

It occurred to us that the alternative *exo-endo* and *exo-exo* isomers should be accessible from the corresponding *trans*-dihydrofuran template. Consequently, we explored isomerization of the *cis*-dihydrofuran ester **6** through enolization and selective reprotonation. Initial attempts using strong base were not successful, affording mainly decomposed material regardless of the nature of the trapping agent. Subsequently, although the use of weaker bases such as Et_3N, EtN^iPr_2, or DBU in either stoichiometric or excess amounts afforded the *trans* isomer, this occurred with both poor conversions and low yields. Fortunately, the use of a catalytic amount of base (≤10 mol %) allowed the isolation of the required *trans* isomer with high selectivity (>95: <5). Diastereomerically pure material could be obtained in 91% yield following simple chromatography.[7] Following reduction with $LiAlH_4$, the resultant unstable dihydrofuranmethanol **11** was treated with 1.1 equivalents of TMSOTf and acetal **10** in DCM at −40 °C to afford the expected *exo-endo*-furofuran acetal **12** as a single stereoisomer, Scheme 2. The stereochemistry was confirmed by a combination of 2D NMR experiments in particular NOESY experiments. Simply allowing the cyclization reaction to warm to room temperature produced the *exo-exo*-2,6-diarylfurofuran core **13** albeit as a 1:2 *endo*/*exo* mixture of acetal stereoisomers in 45% yield after column chromatography.

To complete the synthesis of the furofuran skeleton, it remained to reduce the acetal to the cyclic ether. While, in our initial studies, we had been able to reduce the 2,6-diphenyl isomer **14a** at room temperature using Et_3SiH/$BF_3{\cdot}OEt_2$ with no loss of stereochemical integrity, this was not possible in our synthesis of the *endo-endo*-furofuran epiasarinin **15b**. This is consistent with an earlier report by Pelter et al. who had shown that, under

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(1) Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75−96.
(2) See ref 1 and citations therein.
(3) (a) Brown, R. C. D.; Bataille, C. J.; Bataille, C. J. R.; Bruton, G.; Hinks, J. D.; Swain, N. A. *J. Org. Chem.* **2001**, *66*, 6719−6728. (b) Yoshida, S.; Yamanaka, T.; Miyake, T.; Moritani, Y.; Ohmizu, H.; Iwasaki, T. *Tetrahedron* **1997**, *53*, 9585−9598. (c) Yoshida, S.; Ogiku, T.; Ohmizu, H.; Iwasaki, T. *J. Org. Chem.* **1997**, *62*, 1310−1316. (d) Samizu, K.; Ogasawara, K. *Chem. Lett.* **1995**, 543−544. (e) Pelter, A.; Ward, R. S.; Collins, P.; Venkateswarlu, R.; Kay, I. T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 587−594. (f) Stevens, D. R.; Till, C. P.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1*, **1992**, 185.
(4) Aldous, D. J.; Dalencon, A. J.; Steel, P. G. *Org. Lett.* **2002**, *4*, 1159−1162.
(5) Aldous, D. J.; Dutton, W. M.; Steel, P. G. *Synlett* **1999**, 474−476.
(6) A related intramolecular cationic cyclisation using lactone silyl enol ethers as a terminating group has previously been reported although, in contrast to the strategy outlined in this manuscript, with a 4-methoxyaryl substituents this produces exclusively the *exo* product. See ref 3f.
(7) All new compounds have satisfactory spectroscopic and analytical data.

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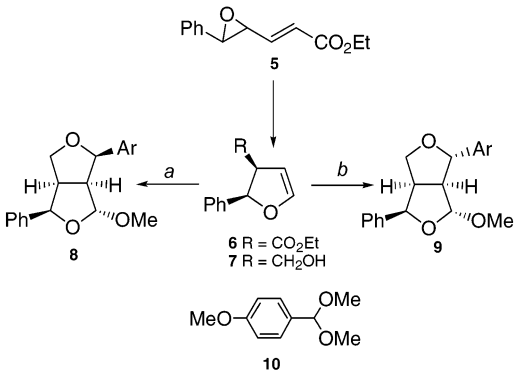
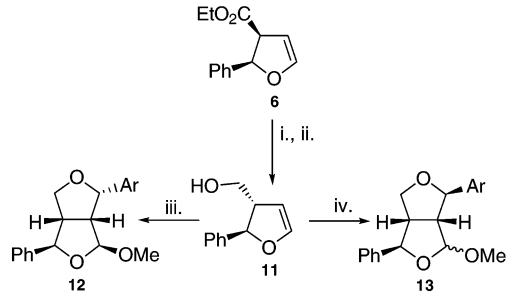
SCHEME 1[a]



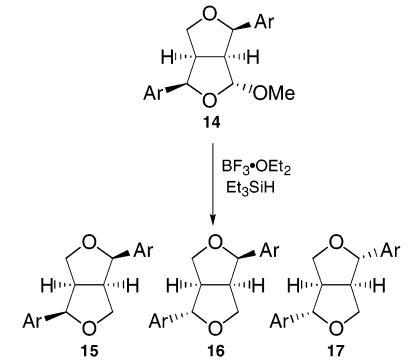
[a] Reaction conditions: (a) **10**, 1.1 equiv of TMSOTf, CH_2Cl_2, −20 °C, 81%; (b) **10**, 1.1 equiv of TMSOTf, CH_2Cl_2, −20 °C to rt, 68% (Ar = 4-$MeOC_6H_4$).

SCHEME 2[a]



[a] Reaction conditions: (i) DBU (cat.), THF, 91%, (ii) $LiAlH_4$, Et_2O, 0 °C, (iii) **10**, 1.1 equiv of TMSOTf, CH_2Cl_2, −40 °C, 53%, (iv) **10**, 1.1 equiv of TMSOTf, CH_2Cl_2, −40 °C to rt, 45% (Ar = 4-$MeOC_6H_4$).

SCHEME 3

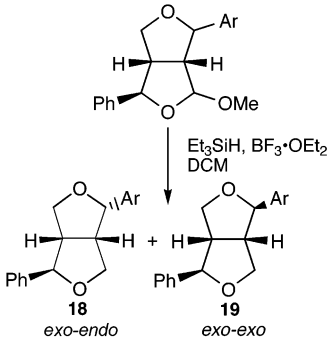


these conditions, an adjacent bridgehead thiomethyl group is required to inhibit isomerization of an *endo*-aryl group.[3e] In the epiasarinin synthesis, efficient reduction with minimal isomerization of the aryl groups was ultimately achieved using lower temperatures and shorter reaction times, Scheme 3.[4]

However, subjecting *endo-endo*-acetal **8** to these "optimized" conditions afforded the *endo-exo*-aryl-substituted furofuran **21**. Ultimately, after considerable variation of reaction time and temperature, we discovered that these substrates undergo a rapid reduction (∼1 min) at −78 °C. Under these conditions, the *exo-endo*-**12**, *exo-exo*-**13**, Table 1, and *endo-exo*-**9**, Table 2, acetal isomers can be selectively reduced to the corresponding 2,6-diarylfurofurans. While, even at this lower temperature there is considerable isomerization of the more crowded *endo-endo* substrate **8**, Table 2, it is possible to isolate the desired *endo-endo*-furofuran **20** following column chromatography. In contrast, reductions at 0 °C afforded a thermodynamic mixture of isomers in high combined yield.[8]

We account for these observations through the mechanistic pathway outlined in Scheme 4. Lewis acid activa-

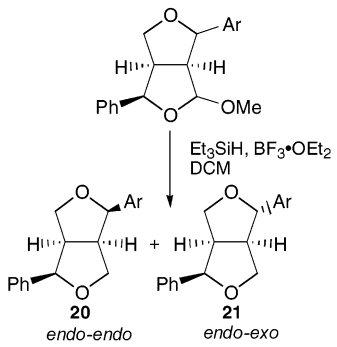
TABLE 1.[a]



	conditions	conversion	18	:	19
12 *exo-endo*	0°C, 1h	100%	26	:	74
	-78°C, 1 min	86%	100	:	0
13 *exo-exo*	0°C, 1 h	100%	26	:	74
	-78°C, 1.25 min	100%	18	:	82

[a] Ar = 4-$MeOC_6H_4$−; ratios and conversions determined by ^1H NMR and GLC of the crude reaction mixture.

TABLE 2.[a]

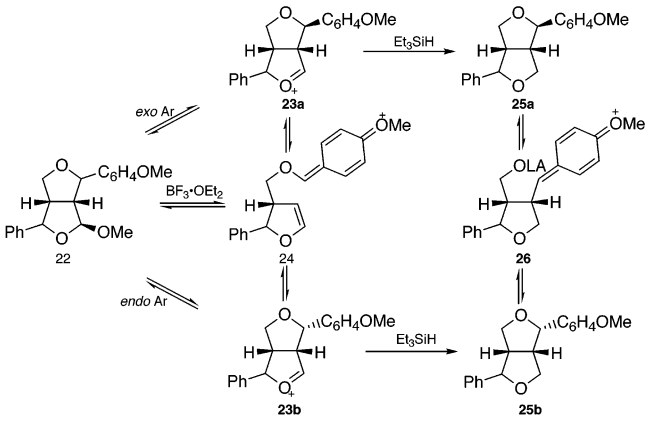


	conditions	conversion	20	:	21
8 *endo-endo*	0°C, 1h	100%	0	:	100
	-78°C, 1 min	73%	40	:	60
9 *endo-exo*	0°C, 1 h	100%	0	:	100
	-78°C, 1.25 min	36%	8	:	92

[a] Ar = 4-$MeOC_6H_4$−; ratios and conversions determined by ^1H NMR and GLC of the crude reaction mixture.

(8) Pelter, A.; Ward, R. S. *Heterocycles* **1994**, *37*, 137−147.

SCHEME 4



tion of the methyl acetal **22** affords oxonium ion **23** that, at low temperatures, is rapidly trapped by Et_3SiH to give the furofuran **25** with retention of stereochemistry. Fragmentation of the bicyclic nucleus can compete with the reduction step to give the stabilized benzylic oxonium ion **24**. This can recyclize to produce either the *endo* **b** or *exo* **a** isomer series. At low temperature, the former is favored and hence the observed formation of *exo-endo*- and *endo-endo*-furofurans, **18** and **20**, from the reduction of *exo-exo*- and *endo-exo*-acetals **13** and **9**, respectively, Tables 1 and 2. Alternatively, isomerization of the furofurans **25** can occur through a similar intermediate **26**, facilitated by the electron-donating *p*-methoxy group. This is a higher energy process and only occurs at significant rates at temperatures greater than −78 °C. The presence of an electron-donating group is essential for isomerization as evidence by the stability of the 2,6-diphenylfurofuran under all these reaction conditions. The enhanced stereochemical stability of epiasarinin **15b** which possesses methylenedioxyphenyl aryl groups compared with the *p*-methoxy congeners **18**−**21** under these acidic conditions is attributed to the fact that the latter compounds can achieve a more favorable orbital overlap between the oxygen lone pair and benzylic carbocation involved in the epimerization process. We speculate that the difference in reactivity and outcomes between the two isomeric series is due to conformational effects enforced by anomeric type interactions.[9] Calculations to verify this are in progress and results of these and further synthetic studies on this important skeletal class of natural products will be reported in due course.

In conclusion, starting from a single vinyl epoxide, it is possible to prepare all four possible isomers of a 2,6-diarylfurofuran with control of the stereochemistry by suitable choice of substrates and reaction conditions.

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Supporting Information Available: Experimental section containing general procedures and characterization of compounds **8**, **9**, **12**, **13**, and **18**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035148Q

(9) Lutz, G.; Hofer, O.; Brader, G.; Kratky, C. *Heterocycles* **1997**, *45*, 287−298.