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Synthesis of 10 stereochemically distinct bis-tetrahydrofuran intermediates for creating a library of 64 asimicin stereoisomers

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ABSTRACT

Stereoselective synthesis of 10 unique bifunctional stereoisomeric adjacent bis-THF intermediates (R = Bz), including **5.1**–**5.4**, **5.7**–**5.9**, **5.11**, and **5.15**–**5.16**, of 16 possible compounds, is described. The key steps used in the synthesis of these compounds included the rhenium(VII) oxide-mediated and the $Co(modp)_2$-catalyzed trans oxidative cyclizations (OCs), the OsO_4-catalyzed cis OC, and the Williamson's type etherification reactions. The remaining six bis-THF intermediates (R = Bn) can be prepared from **5.7**–**5.9**, **5.11**, and **5.15**–**5.1**6 (R = Bz) in two steps, including protection of the free alcohol as benzyl ether followed by the benzoate deprotection. These intermediates should provide access to all 64 asimicin stereoisomers and their analogs.

Asimicin-type adjacent bis-tetrahydrofuran (bis-THF) acetogenins, such as asimicin, bullatacin, and trilobacin, are highly potent cytotoxic molecules.[1] Arguably, cytotoxicity of these adjacent bis-THF acetogenins, and their inhibitory effect on the mitochondrial enzyme, complex I, could depend upon the stereochemistry of their bis-THF core, including the adjacent hydroxyl functions.[1–3] In order to determine such stereochemistry–activity relationships, we decided to synthesize all 64 stereoisomeric asimicins, (**1.1**–**1.16**)(**a**–**d**), which are diastereomeric in the bis-THF core (Fig. 1).[4] We, as well as others, have developed several strategies for the synthesis of the adjacent bis-THF acetogenins, which could also be applied to the asimicins library.[5,6] In particular, a bidirectional approach employing intermediate **5**'s (Fig. 1) appeared the most efficient strategy, in that the latter could be alkylated with the alkyl and butenolide-alkyl side chains at two ends to rapidly afford not only the complete asimicin library but also their analogs.[2,6d,7,8] In fact, by modifying such a bidirectional approach, we successfully prepared eight stereoisomeric asimicins (**1.1a**–**d** and **1.4a**–**d**) using **5.1** and **5.4**, respectively, as the key intermediates.[2] To synthesize the remaining 56 stereoisomeric asimicins using this bidirectional approach, 14 bis-THF intermediates **5.2, 5.3,** and **5.5**–**5.16** or their equivalents, such as **5.5′**-**5.16′** (Fig. 1) were needed. In this Letter, we report the synthesis of eight more stereochemically distinct bis-THF intermediates, including **5.2, 5.3**, **5.7**–**5.9**, **5.11**, and **5.15**–**5.16**, which together with **5.1** and **5.4** can afford all stereoisomeric **1**'s using a bidirectional approach. We also hypothesize that a large library of stereoisomeric **1**'s and their analogs can be best obtained from **5**'s using a less or nonselective synthetic approach coupled to an efficient chromatographic separation technique.

'Only 10 stereochemically distinct bis-THF intermediates among compounds **5.1**–**5.16** were essential for the asimicin's library synthesis' became evident from a comparison of compounds **5.5**, **5.6**, **5.9**, **5.11**, **5.13**, and **5.14** to **5.7**, **5.8**, **5.10**, **5.12**, **5.16**, and **5.13**, respectively. Each compound-pair upon base hydrolysis would give a common diol, and therefore each pair or their equivalents should be achievable from a common source. For example, the diols **5.5-D** and **5.7-D** possessed identical stereochemistry, and one could certainly convert compound **5.7** to **5.5** equiv, such as **5.5′**, or vice versa. For this, the free hydroxyl function in compound **5.7** would undergo benzyl protection followed by hydrolysis to remove the benzoate ester giving **5.5′**. In this manner, compounds **5.6′**, **5.9′**, **5.11′**, **5.13′**, and **5.14′** could also be prepared from **5.8**, **5.10**, **5.12**, **5.16**, and **5.15**, and compounds **5.7′**, **5.8′**, **5.10′**, **5.12′**, **5.15′**, and **5.16′** from **5.5**, **5.6**, **5.9**, **5.11**, **5.14**, and **5.13**, respectively (Scheme 1).

Synthesis of compounds **5.2, 5.3**, **5.7**–**5.9**, **5.11**, and **5.15**–**5.16** are shown in Scheme 2 and Table 1. We used Sharpless asymmetric dihydroxylation (AD)[9] reaction to introduce chirality in the starting materials, and a combination of the oxidative cyclization (OC), and the Williamson's type etherification reactions to prepare the THF rings stereoselectively. The Re(VII) oxide-mediated[10] and/or Mukaiyama's $Co(modp)_2$-catalyzed[11] trans oxidative cyclization (OC) reactions, (i.e., Re-OC and/or Co-OC) and Donohoe's Os(VI) oxide-catalyzed cis OC (i.e., Os-OC),[12] were used to prepare THF rings with trans and cis configurations. Thus, compounds **5.2** and **5.3** were prepared in 55–60% yields starting with diols **3.1** and **3.2** in four steps, as described earlier for their enantiomers, **5.1** and **5.4**. First, the diol **3**'s were reacted with MsCl in pyridine giving dimesylates

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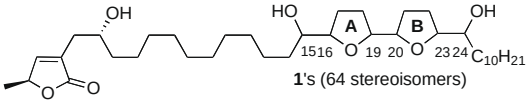
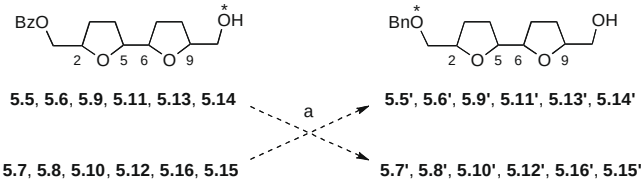


5.1-**5.4**, R = Bz
(**5.1**-**5.4**)-**D**, R = H

5.5-**5.16**, R = Bz
5.5'-**5.16'**, R = Bn
(**5.5**-**5.16**)-**D**, R = H

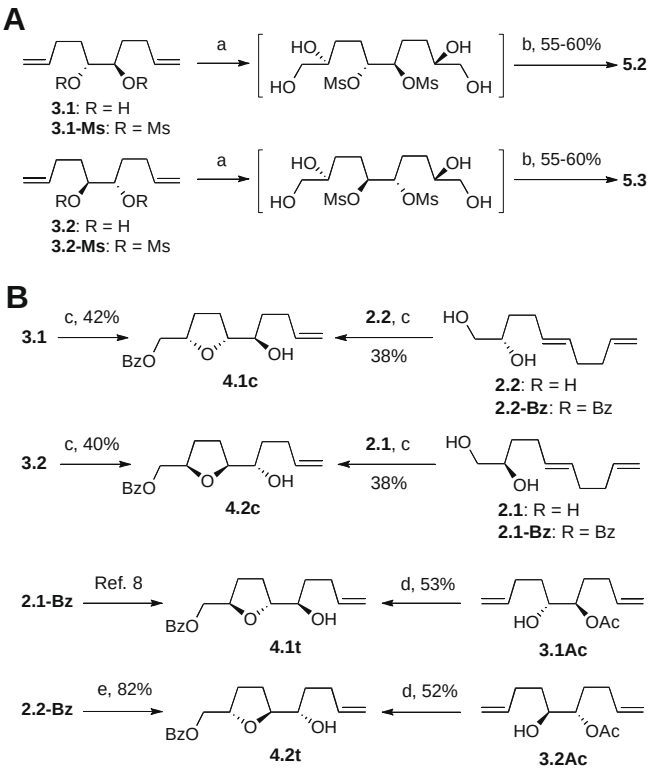
Relative stereochem. A,B rings		absolute[b] stereochem.	asimicin[a] stereoisomers	bis-THF compounds
19,20 (or 5,6) *threo*	*trans*,*trans*	*R*,*R*,*R*,*R* *S*,*S*,*S*,*S*	**1.1a-d** **1.2a-d**	**5.1** **5.2**
	cis,*cis*	*S*,*R*,*R*,*S* *R*,*S*,*S*,*R*	**1.3a-d** **1.4a-d**	**5.3** **5.4**
	trans,*cis*	*R*,*R*,*R*,*S* *S*,*S*,*S*,*R*	**1.5a-d** **1.6a-d**	**5.5** or **5.5'** **5.6** or **5.6'**
	cis,*trans*	*S*,*R*,*R*,*R* *R*,*S*,*S*,*S*	**1.7a-d** **1.8a-d**	**5.7** **5.8**
19,20 (or 5,6) *erythro*	*trans*,*trans*	*R*,*R*,*S*,*S* *S*,*S*,*R*,*R*	**1.9a-d** **1.10a-d**	**5.9** **5.10** or **5.10'**
	cis,*cis*	*S*,*R*,*S*,*R* *R*,*S*,*R*,*S*	**1.11a-d** **1.12a-d**	**5.11** **5.12** or **5.12'**
	trans,*cis*	*R*,*R*,*S*,*R* *S*,*S*,*R*,*S*	**1.13a-d** **1.14a-d**	**5.13** or **5.16'** **5.14** or **5.15'**
	cis,*trans*	*S*,*R*,*S*,*S* *R*,*S*,*R*,*R*	**1.15a-d** **1.16a-d**	**5.15** **5.16**

Figure 1. Structure of the stereoisomeric asimicins (**1.1**–**1.16**)(**a**–**d**), the bis-THF precursors (**5.1**–**5.16**) and their equivalents (**5'**)'s, and the bis-THF diols, **5.*x*-D**'s. [a]All **a**–**d** series of compound **1**'s possess 15*R*,24*R*, 15*S*,24*R*, 15*R*,24*S*, and 15*S*,24*S*, respectively. [b]The absolute configurations for C-16, -19, -20, and -23, and C-2, -5, -6, and -9 in compounds **1**'s and **5**'s, respectively, are shown from left to right. For example, the absolute configurations of compounds **1.5** and **5.5** are 16*R*,19*R*,20*R*,23*S* and 2*R*,5*R*,6*R*,9*S*, respectively.



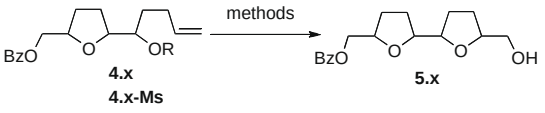
Scheme 1. Proposed interconversion of bis-THF intermediates, **5.*x*** (R = Bz) to **5.*x*'** (R = Bn). ⁎sign shows the specific oxygen being protected with benzyl group. Reagents: (a) (i) BnBr, NaH, DMF, (ii) LiOH, aq MeOH–THF.

3.1-Ms and **3.2-Ms**. Subsequently, Sharpless AD reaction of the dimesylates using AD-α gave tetrols, which underwent the etherification reaction by refluxing in pyridine. Finally, mono-protection of the resulting bis-THF diols using benzoyl chloride (BzCl) afforded **5.2** and **5.3** (Scheme 2A). Like compound **5.1**, we also prepared **5.2** in a stepwise manner using *trans* mono-THF intermediate **4.2t**. In fact, all other intermediates, including **5.7**–**5.9**, **5.11**, and **5.15**–**5.16**, were prepared via the mono-THF intermediates **4.1c**, **4.2c** and **4.1t**, **4.2t** (Scheme 2B, and Table 1). The *trans* mono-THF intermediates, **4.1t** and **4.2t**, were prepared by the Co-OC reaction of the mono-protected derivatives of diols **3.1** and **3.2**, that is, **3.1Ac** and **3.2Ac**, respectively, followed by deacetylation and selective benzoylation of the primary alcohol.[6d] Alternatively, the *trans* mono-THF compounds, **41t** and **4.2t**, were prepared by Re-OC, but not by Co-OC, reaction of **2.1-Bz** and **2.2-Bz**.[8] The *cis* mono-THF compounds **4.1c** and **4.2c** were prepared using Os-OC reaction of diols **3.1** and **3.2**, respectively, followed by regioselective mono-protection of the primary alcohol using BzCl. Diols **2.2** and **2.1** also afforded **4.1c** and **4.2c** in a similar manner.



Scheme 2. Stereoselective synthesis of (A) bis-THF intermediates **5.2**–**5.3**, and (B) the mono-THF compounds **4.1c**–**4.2c** and **4.1t**–**4.2t**. Reagents and conditions: (a) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, (ii) AD-mix-α, *tert*-BuOH, H_2O; (b) (i) Py, 140 °C, (ii) BzCl, Et_3N, CH_2Cl_2; (c) (i) K_2OsO_4 (cat), Me_3NO, TFA, H_2O–acetone, 50 °C, (ii) step b (ii); (d) (i) $Co(modp)_2$, TBHP, *i*PrOH, (ii) aq LiOH, THF-MeOH, (iii) step b (ii); (e) $TFAOReO_3$, TFAA, then aq $NaHCO_3$, H_2O_2.

Table 1
Stereoselective syntheses of the bis-THF compounds from the mono-THF intermediates[a]



Product **5.*x***	Intermediate **4.*x***	Methods	Yields (from **4.*x***)
5.1	**4.1t**	A	67
5.2	**4.2t**	A	63
5.7	**4.1c**	A	82
5.8	**4.2c**	A	78
5.9	**4.1t**	B,C	58
5.11	**4.1c**	B,D	49
5.15	**4.1c**	B,C	55
5.16	**4.2c**	B,D	53
5.10	**4.2t**	B,D	—[b]
5.12	**4.2c**	B,C	—[b]
5.13	**4.1t**	B,D	—[b]
5.14	**4.2t**	B,C	—[b]

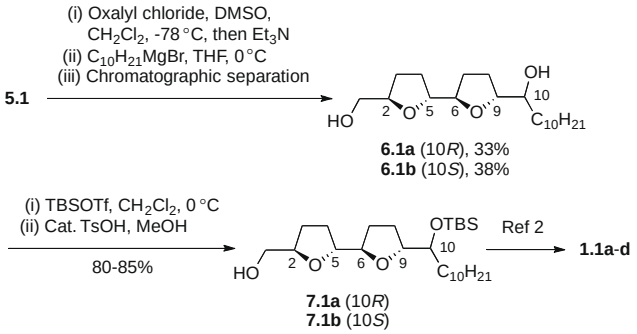
[a] Methods: (A) $Co(modp)_2$, TBHP, *i*PrOH, 50 °C, 2–4 h; (B) MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h; (C) (i) AD-mix-α, *tert*-BuOH, H_2O, 0 °C, 16 h, then aq Na_2SO_3, (ii) pyridine, 140 °C, 2 h; (D) (i) AD-mix-β, *tert*-BuOH, H_2O, 0 °C, 16 h, then aq Na_2SO_3, 0.5 h; (ii) step C (ii).
[b] Reaction not performed.

Intermediates **4.1c**–**4.2c** and **4.1t**–**4.2t** were next converted to bis-THF intermediates either using second OC reaction, or using three steps (i) mesylation of the free alcohol function, (ii) dihydroxylation of the terminal olefin, and (iii) Williamson's-type

etherification of the resulting dihydroxymesylate in a sequence (Table 1). Thus, using Co-OC reaction, the *trans* mono-THF alcohols **4.1t** and **4.2t** were converted to *trans*, *trans* bis-THF alcohols **5.1** and **5.2**, and the *cis* mono-THF alcohols **4.1c** and **4.2c** to *cis*, *trans* bis-THF alcohols **5.7** and **5.8**. In all compounds, the new *trans* THF ring was formed exclusively. As expected, these mono-THF intermediates did not undergo second cyclization using Os-OC reaction, and our attempt to prepare compounds **5.3**–**5.6** using *cis* and *trans* **4**'s by Os-OC reaction was unsuccessful. The remaining four bis-THF intermediates, which possessed an *erythro* configuration between C-5,C-6 centers and the *trans* or *cis* B-ring, namely, **5.9**, **5.11**, **5.15**, and **5.16**, were all prepared using the above-described three steps from the appropriate **4**'s and AD ligands. The Phal-DHQ ligand was used in the AD reaction to prepare intermediates **5.9** and **5.15**, which possessed '*S*' stereochemistry, and Phal-DHQD for intermediates **5.11** and **5.16**, with '*R*' stereochemistry for C-9 center. Using the above-described strategy, one could also prepare four of the remaining six compounds, including **5.10**, **5.12**, **5.13**, and **5.14**, which are indeed the enantiomers of compounds **5.9**, **5.11**, **5.16**, and **5.15**, respectively, from the mono-THF intermediates, **4.1t**, **4.2t,** or **4.2c** (see: Table 1 bottom section).

All bis-THF compounds, **5**'s, prepared in this manner, were most likely to bear the desired configuration, yet we also confirmed them by comparing the ^{1}H and ^{13}C NMR spectral data of these compounds as well as the corresponding bis-THF diols, **5.*x*-D**'s (See Fig. 1). The latter compounds were either obtained en route to the synthesis of **5**'s, as in **5.1**-**5.4**, or by hydrolyzing the benzoate-protecting group in the remaining six bis-THF intermediates, **5.7**–**5.9**, **5.11**, and **5.15**–**5.16**. First, we found that compounds **5.1**, **5.3**, **5.7**, and **5.15** showed ^{1}H and ^{13}C NMR spectra identical to their enantiomers **5.2**, **5.4**, **5.8**, and **5.16**, respectively, but different with respect to compounds **5.9** and **5.11**. Next, one compound from the enantiomeric pairs, including **5.1**, **5.3**, **5.7**, and **5.15**, and compounds **5.9** and **5.11**, were chosen and their diol analogs, that is, **5.1-D**, **5.3-D**, **5.7-D**, **5.9-D**, **5.11-D**, and **5.15-D**, were obtained either from their precursor pools (in **5.1-D** and **5.3-D**) or through base hydrolysis, and analyzed. As expected, all six diols showed distinct ^{13}C NMR spectral data; and the symmetrical bis-THF diols, **5.1-D**, **5.3-D**, **5.9-D**, and **5.11-D**, showed only five C signals, whereas the unsymmetrical diols, **5.7-D** and **5.15-D**, showed 10 C signals (See Supplementary data). The data, together with the fact that compounds **5.1** and **5.2** were prepared in two different ways, assured us that all **5**'s possessed the expected configurations.

With the stereoisomeric intermediate **5**'s in hand, one can convert them to the desired asimicin library or their analogs, as well as numerous related bis-THF acetogenins, including goniodenin- and glabracin A-type compounds,[1] which unlike asimicin possess only one hydroxy function adjacent to the bis-THF ring. In the context of the asimicin library, we can use the previously described synthetic scheme and optimize the Carreira's enantioselective alkynylation reaction[13] to give stereochemically pure **1**'s. Alternatively, we argue that the library of **1**'s can be prepared rapidly from **5**'s using a combination of stereoselective and the nonstereoselective methods. For example, in one approach, the aldehyde of compound **5.1** underwent nonstereoselective alkylation using decyl-magnesium bromide giving an essentially 1:1 mixture of compounds **6.1a** and **6.1b**. The latter was separated and protected as di-TBS ether and then selectively deprotected to give compounds **7.1a** and **7.1b** (Scheme 3), which were previously converted to four bis-THF acetogenins, **1.1a**–**d**. Alternatively, a mixture of **7.1a** and **7.1b** can also undergo Carreira's alkynylation reaction using a chiral ligand giving a mixture of two isomeric compounds **1.1**'s after deprotection and hydrogenation. If the Carreira's alkylation is less selective, one can get a mixture of two **1.1**'s each from pure **7.1a** and **7.1b**, or all four **1.1**'s as a mixture of two major and two minor products, in one set of reactions. In this manner, 32 pairs or 16 set



Scheme 3. A combined nonselective and stereoselective approach to the synthesis of stereoisomeric asimicins.

of four of the stereoisomeric **1**'s can be prepared and separated giving all 64 **1**'s. Analysis of the compounds can be facilitated by carefully comparing the ratios of the products in each step using ^{1}H NMR and after purification.

In conclusion, 10 unique bis-THF intermediates, **5**'s, were prepared starting with the readily available diols **2**'s or **3**'s in good yields. The synthetic processes used to produce **5**'s were simple and reproducible, and could be carried out on a large scale without extra precautions. The bis-THF intermediates **5.1**–**5.4**, **5.9**, **5.11**, **5.15**, and **5.16**, which were prepared from the stereochemically enriched mono-THF compounds, **4**'s, (82% ee prepared from **2**'s and 92% ee from **3**'s) and using an AD step, were obtained with more than 98% enantiomeric purity after purification, whereas compounds **5.7**–**5.8** retained the enantiomeric purity identical to **4**'s. We expect that a complete library of 64 stereoisomeric asimicins, and other related bis-THF acetogenins can be prepared from these 10 bis-THF intermediates rapidly using a combination of the stereoselective and nonstereoselective methods, and obtained in enantiomerically pure form by purification using HPLC.

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Supplementary data

Supplementary data (spectroscopic data and experimental procedures) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.082.

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