Tetrahydropyranes

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Stereodivergent Synthesis of Functionalized Tetrahydropyrans Accelerated by Mechanism-Based Allylboration and Bioinspired Oxa-Michael Cyclization

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Abstract: *A stereodivergent strategy enabled by bioinspired oxa-Michael cyclization was developed for the synthesis of functionalized tetrahydropyrans on the basis of the inherent symmetry in 1,3-diols, the symmetries of which were tunable by stereoselective hydroboration of an allene with a variety of alkylborane reagents and subsequent allylation of an aldehyde. The mechanism-based utilization of monoalkyl borane in the hydroboration and allylation cascade is unprecedented.*

Functionalized tetrahydropyrans (THPs) are recurring motifs in numerous biologically significant natural products, such as lasonolide A (**1**), ambruticin S (**2**), and pederin (**3**) (Figure 1 a).[1] A pyran-cyclase-catalyzed oxa-Michael reaction[2] was proposed to construct THPs, although the detailed enzymology remains unknown.[3] The past several decades have seen a variety of synthetic methods for the efficient construction of THPs.[4] For instance, during the synthesis of lasonolide A (**1**), a potent anticancer marine natural product, the methods used to access the THP ring were diverse.[5] The known approaches, however, face the challenge of stereodiversification of the four stereogenic centers in each THP, and would be detrimental when a structure–activity relationship (SAR) study is undertaken. With our continued interest in polyketide synthesis, we became aware of a general approach to access all stereoisomers of substituted THPs. This strategy should meet several criteria: 1) a flexible method to access three contiguous chiral centers with good stereoselectivity; 2) facile accessibility of both *cis*- and *trans*-stereoisomers of THP; and 3) a short and reliable synthetic route. To this end, the A ring bearing a quaternary carbon center in the lasonolides was selected to demonstrate the generic and rapid access to the stereovariants of the hydropyran ring.

We envisioned that a bioinspired oxa-Michael addition[6] would simplify the construction of two hydropyrans in lasonolide A and its congeners if two electron-deficient alkenes were preinstalled at C23 and C7. An inherent symmetry in such THPs further guided us to design the skipped polyol **4**, which bears substituents at the central carbon atom and different distal protecting groups (e.g., P^1 and P^2; Figure 1 b). Accordingly, stereovariants of a given THP were envisioned to be constructed by propagation of a latent symmetry element through processing of the terminal functional groups (OP^1 or OP^2) by means of a bioinspired oxa-Michael cyclization. The access would rely on the selective installation of α,β-unsaturated esters on either the left or right side of **4** to allow the late Michael addition to occur.

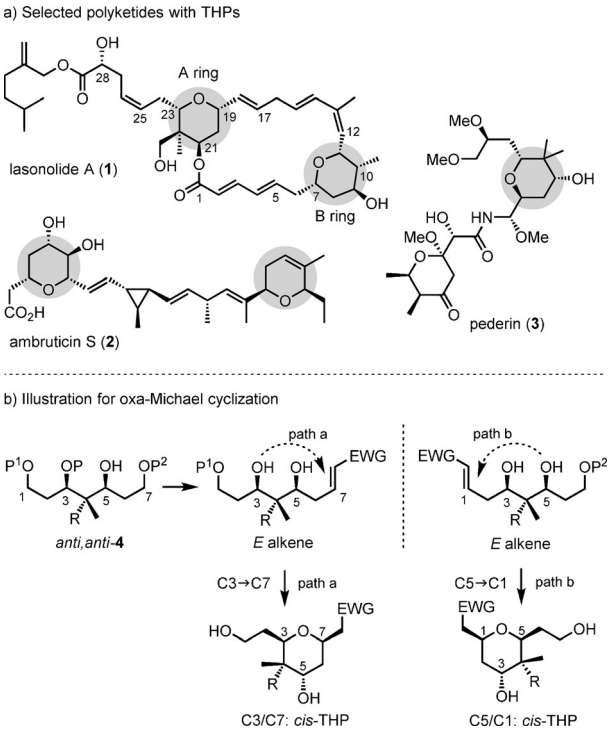

Figure 1. a) Tetrahydropyrans in selected polyketides (highlighted in grey; carbon atom numbering adapted from the original assignment). b) An illustration of oxa-Michael cyclization (*anti*,*anti*-**4** as example). P, P^1, P^2 = protecting groups, EWG = electron withdrawing group.

To begin with, the first level of synthesis would require a stereodefinable allylation initiated from the hydroboration of the allene **5** to access all possible diastereoisomers of **4** (Scheme 1). It was known that 9-borabicyclo[3.3.1]nonane (9-BBN) would deliver *syn*,*syn*-**4a** with good diastereoselectivity (84% yield, d.r. 10:1) via an *E*-allylborane, which is derived from thermodynamic hydroboration of the allene (40 °C for

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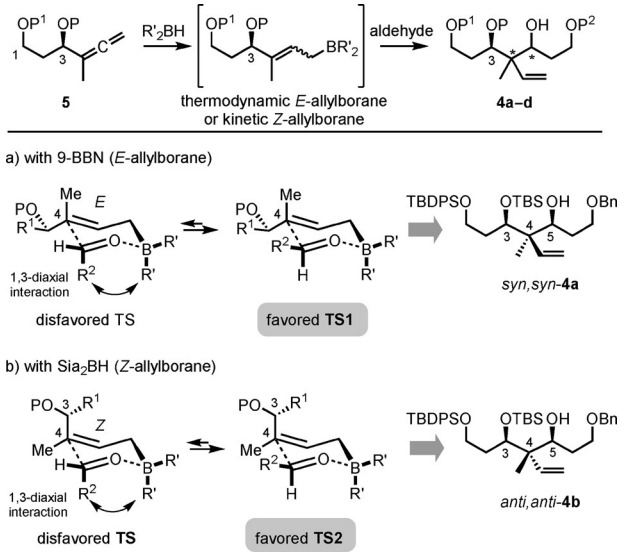
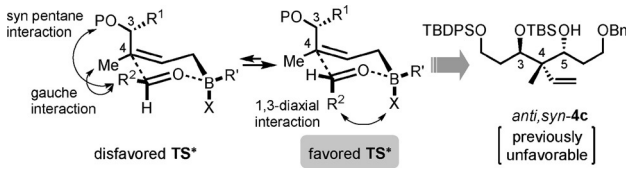


Scheme 1. Stereochemical rationale of allylboration with *E*- and *Z*-allylborane derived from thermodynamic and kinetic conditions, respectively. Bn = benzyl, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.

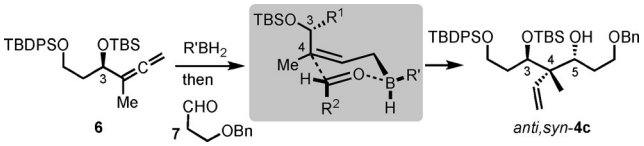
4 h) (Scheme 1 a).[7,8] Although bis(cyclohexyl)borane (Chx_2BH) was effective in the work of Ariza and co-workers for the preparation of simpler *anti,anti*-1,3-diols in a kinetic fashion (0 °C, 3 h),[9] the hydroboration of the **5** was slow, and at an elevated temperature formation of *syn,syn*-**4a** increased because of the increased presence of the *E*-allylborane arising from a 1,3-boratropic shift.[10] Fortunately, upon surveying other boranes and varying the reaction parameters (see the Table S2 in the Supporting Information),[8] disiamylborane (Sia_2BH) was identified as a superior kinetic borane reagent to afford *anti,anti*-**4b**, via a favorable transition state with *Z*-allylborane (**TS2** in Scheme 1 b), in 90 % yield and excellent diastereoselectivity (d.r. > 15:1).

Access to either *anti,syn*-**4c** or *syn,anti*-**4d** was not nearly as facile as that of the two previously described diastereomers. Mechanistically, during the hydroboration of the kinetically formed *Z*-allylborane, the severe 1,3-diaxial interaction between the alkyl chain R^2 and the R′ in borane enforces an equatorial R^2 in the favorable transition state, which gives *anti,anti*-**4b** (Scheme 1 b). However, for the formation of *anti,syn*-**4c**, the R^2 group should reside at the axial position during the allylation via **TS*** (Scheme 2), in which the detrimental $A^{1,3}$ strain could be attenuated by introducing a less sterically hindered group (X) on the borane. Hydrogen is certainly an ideal alternative. Inspired by the Brown



Scheme 2. Proposed transition states for *anti,syn*-**4c** with *Z*-allylborane: *syn*-pentane interaction and gauche interaction versus 1,3-diaxial interaction.

Table 1: Sequential hydroboration and allylation with monoalkyl boranes.[a]



Entry	Borane (equiv)	*T* [°C]	Conv [%][b]	Yield [%][c]	d.r.[d]
1	(−)-IpcBH$_2$ (2.0)	0→RT	77 (4 h)	43	2.5:1
2	(+)-IpcBH$_2$ (2.0)	0	>95 (1.4 h)	n.d.	1.7:1
3	ThexBH$_2$ (2.0)	0	>95 (4 h)	45	4.5:1
4	ThexBH$_2$ (1.3)	0	>95 (2 h)	70	4.0:1
5	ThexBH$_2$ (1.1)	0	75 (4 h)	n.d.	3.2:1

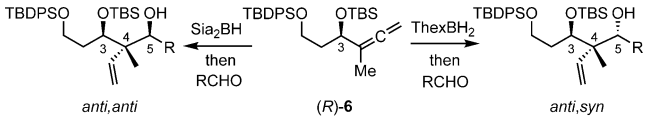
[a] Reaction conditions: (*R*)-**6** (0.73 mmol), aldehyde **7** (1.5 equiv), CH_2Cl_2 (1.4 mL). [b] Conversion was determined by ^{1}H NMR spectroscopy in $CDCl_3$; the reaction time (hours) is given within parentheses. [c] Yield of isolated product. [d] Ratio of the major diastereomer to minor diastereomers. Determined by ^{1}H NMR spectroscopy in $CDCl_3$. n.d. = not determined.

hydroboration with monoalkyl borane,[11] a freshly liberated (−)-IpcBH$_2$ was quickly subjected to the subsequent hydroboration of the allene **6**,[12] and then the aldehyde **7** was added at 0 °C (Table 1). The allylboration proceeded smoothly to deliver the desired *anti,syn*-**4c** in 43 % yield (77 % conversion) after work-up (entry 1). The antipode of (−)-IpcBH$_2$ resulted in the desired product in a lower diastereoselectivity (d.r. 1.7:1), but the reaction proceeded at a faster rate (entry 2). Further optimization revealed that in situ generated 2,3-dimethyl-2-butylborane ($ThexBH_2$) was a superior monoalkyl borane reagent and delivered *anti,syn*-**4c** in good diastereoselectivity (d.r. 4:1; entry 4). Although the selectivity could be slightly increased, the low yields of the isolated products indicated the occurrence of side reactions when 2 equivalents of $ThexBH_2$ was used (entry 3). Additional decrease in the amount of borane only resulted in lower conversion and selectivity (entry 5). Although reaction conditions remain to be optimized, this unprecedented chemistry allowed us to isolate the desired stereotriad in 70 % yield (entry 5). The possible syn-pentane interaction and gauche effect enforce the equatorial alkyl chain of **7** to stay in an axial position as shown in **TS*** (Scheme 2), and thus favorably affords *anti,syn*-**4c**.[13]

Given the encouraging allylboration to access distereoisomers of 1,3-diols, more alkyl aldehydes were preliminarily surveyed (Table 2). Generally good to excellent d.r. values were achieved with Sia_2BH (**4ba–bc**). The previously unfavorable *anti,syn* isomer obtained with a monoalkyl borane in moderate selectivity remains valuable although further optimization is needed (**4ca–cc**).

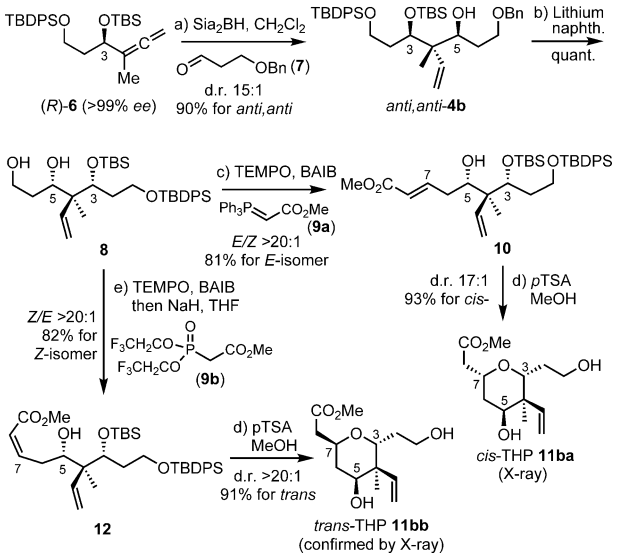
With **a–c** in hand, the subsequent removal of the benzyl group in *anti,anti*-**4b** by the Liu-Shia protocol[14] gave the diol **8** (Scheme 3), which was subjected to the Vatèle one-pot[15] TEMPO/BAIB oxidation and Wittig olefination to afford the ester **10** in 81 % yield (*E*/*Z* 20:1). The subsequent oxa-Michael cyclization in the presence of *p*-tolylsulfonic acid (*p*TSA) delivered the desired *cis*-THP **11ba**, whose stereogenicity was unambiguously established by X-ray analysis.[16] The compound **12** was isolated in 82 % yield as a single isomer

Table 2: Allylboration of other alkyl aldehydes with Sia_2BH and $ThexBH_2$.[a]



Entry	RCHO	Sia_2BH	$ThexBH_2$
1	Ph–CHO (**7a**)	*anti*,*anti*-**4ba**, 73%, d.r. 7:1 [b]	*anti*,*syn*-**4ca**, 61%, d.r. 2.1/1 [b]
2	CHO (**7b**)	*anti*,*anti*-**4bb**, 91%, d.r. >20:1	*anti*,*syn*-**4cb**, 64%, d.r. 2.4:1
3	CHO (**7c**)	*anti*,*anti*-**4bc**, 81%, d.r. 9:1	*anti*,*syn*-**4cc**, 69%, d.r. 3.5:1

[a] The above reactions were conducted with Sia_2BH and $ThexBH_2$ under the optimal reaction conditions described in the Supporting Information. [b] Yield is that of the isolated pure product.



Scheme 3. Construction of the *cis*-THP **11ba** and *trans*-THP **11bb**: a) Sia_2BH (2.5 equiv), CH_2Cl_2, 0 °C, 3 h; **7** (1.5 equiv), −78 °C, 3 h, d.r. 15:1, 90% for *anti*,*anti*-isomer **4b**; b) lithium (12.0 equiv), naphthalene (16.0 equiv), THF, −40 °C, 1.5 h, quant.; c) TEMPO (0.1 equiv), BAIB (1.2 equiv), CH_2Cl_2, RT, 5 h; then **9a** (1.5 equiv), RT, *E*/*Z* > 20:1, 90% for (*E*)-**10**; d) *p*TSA (1.5 equiv), MeOH, reflux, 20 h, d.r. 17:1, 93% for **11ba**; reflux, 4 h, d.r. > 20:1, 91% for **11bb**; e) TEMPO (0.1 equiv), BAIB (1.2 equiv), CH_2Cl_2, RT, 4 h; **9b** (3.0 equiv), NaH (3.0 equiv), THF, −78 °C, 4 h, *Z*/*E* > 20:1, 82% for (*Z*)-**12**. BAIB = bis(acetoxy)-iodobenzene, TEMPO = 2,2,6,6-tetramethylpiperidine oxide, *p*TSA = *para*-toluenesulfonic acid, THF = tetrahydrofuran.

by introducing a *Z* alkene through a similar procedure with the Still–Gennari phosphate **9b**.[17] The following cyclization under identical reaction conditions afforded the *trans*-THP **11bb**, a C7-epimer of **11ba**, in 91% yield.[18] The high diastereoselectivity for the cyclization of the *Z*-configured α,β-unsaturated ester **12** indicated an alternative mechanism may occur, and differs from an allylic cationic species as is generally adopted in precedented Brønsted acid promoted oxa-Michael cyclizations.[4e,6b] It is assumed that a boatlike or twist boatlike transition state might be feasible so that all bulky groups reside in equatorial positions as compared to the chairlike conformation, which may be destabilized by severe steric repulsions (Figure 2).

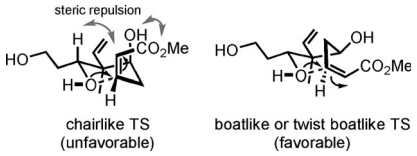
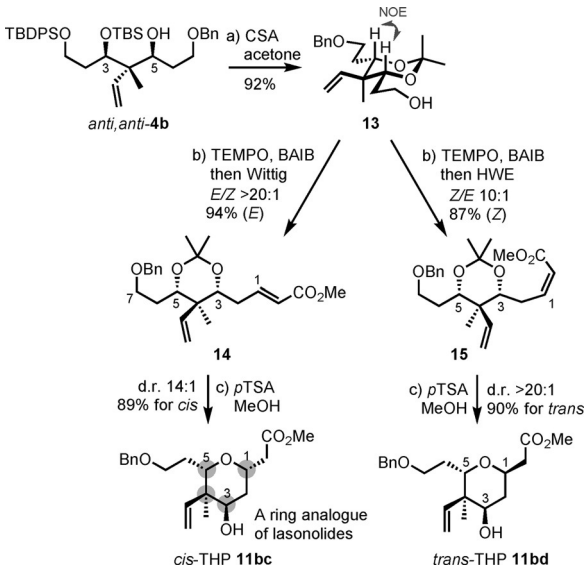


Figure 2. Proposed pathway for acid-promoted oxa-Michael cyclization.

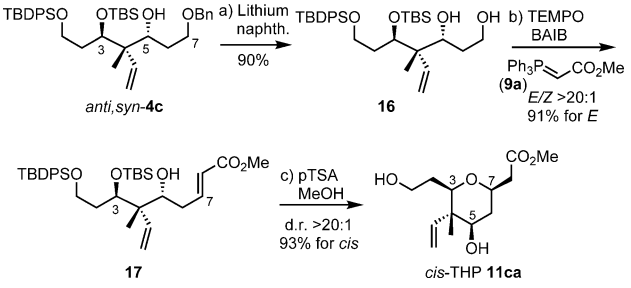
The inherent σ-symmetry in *anti*,*anti*-**4b** would enable a reversed oxa-Michael addition to generate a stereoisomer of **11ba** if the deprotection process could be readily altered. With this notion in mind, a complete removal of two silyl groups and simultaneous formation of the acetonide gave the 1,3-dioxane **13**[8] in excellent yield (Scheme 4). The following one-pot oxidation and olefination smoothly afforded the *E*-configured α,β-unsaturated ester **14** in 94% yield. Finally, the aforementioned protocol for the oxa-Michael cyclization proved to be reliable to give the *cis*-THP **11bc** as the major stereoisomer (d.r. > 14:1) in just four steps and 69% overall yield from (*R*)-**6**. The four stereocenters of **11bc** were identical to the A ring (from C19 to C23) in **1**. The vinyl



Scheme 4. Construction of the *cis*-THP **11bc** and *trans*-THP **11bd**: a) CSA (2.0 equiv), acetone, reflux, 35 h; 92%; c) TEMPO (0.1 equiv), BAIB (1.2 equiv), CH_2Cl_2, RT, 5 h; **9a** (1.5 equiv), RT, 3 h, *E*/*Z* > 20:1, 94% for (*E*)-**14**; **9b** (1.5 equiv), NaH (1.5 equiv), THF, −78 °C, 1 h, *Z*/*E* 10:1, 87% for (*Z*)-**15**; c) *p*TSA (1.5 equiv), MeOH, reflux, 20 h, d.r. 14:1, 89% for **11bc**; reflux, 4 h, d.r. > 20:1, 90% for **11bd**. CSA = camphorsulfonic acid.

group has the potential to be revealed as a hydroxymethyl group at a late stage of the synthesis of **1**.[8] This practical synthesis sequence was further exemplified in the cyclization of **15**, which readily arose from **13** by oxidation/Horner–Wadsworth–Emmons (HWE) olefination. The synthesis route illustrated here offers a complete platform to access four diastereomers of the hydropyran derived from *anti*,*anti*-**4b** (see Figure S1).

With successful access to the stereovariants of THP from **4b**, we decided to complete the stereoisomer derived from *anti*,*syn*-**4c** by this deprotection/chain elongation/cyclization strategy (Scheme 5). After removal of the benzyl group, the



Scheme 5. Three-step synthesis of The *cis*-THP **11ca** from *anti*,*syn*-**4c**: a) lithium (12.0 equiv), naphthalene (16.0 equiv), THF, −78 °C, 4 h, 90%; b) TEMPO (0.1 equiv), BAIB (1.3 equiv), CH_2Cl_2, RT; **9a** (1.5 equiv), RT, *E*/*Z* > 20:1, 91%; c) *p*TSA (1.5 equiv), MeOH, reflux, 20 h, d.r. > 20:1, 93%.

selective oxidation of the resulting primary alcohol underwent a clean conversion and the following Wittig olefination proceeded smoothly to give the *E*-alkene **17** in 91% yield. The *cis*-THP **11ca** was isolated in excellent yield with a ratio of over 20:1 under acidic conditions. The total synthesis comprises four steps with 53% overall yield from (*R*)-**6**.

In summary, we have disclosed a mechanism-based hydroboration of allenes and subsequent allylation to enable the stereoselective synthesis of *syn*,*syn*-, *anti*,*anti*- and *anti*,*syn*-1,3-diols, which were further used in an oxa-Michael cyclization for the stereodivergent synthesis[19] of functionalized THPs. The unprecedented monoalkyl allylborane in the hydroboration of allenes and subsequent allyllation implies a novel stereocontrol mechanism which deserves additional detailed investigation. With the established kinetic or thermodynamic hydroboration of allenes, this tactic formed all stereoisomers of the hydropyrans (16 isomers in principle) in just four steps with overall yields of 53 ~ 69% from the given chiral allenic alcohol. The practicality of individual transformations as well as the orthogonal reactivities of versatile functional groups provides a route to establish stereocongeners of THPs within biologically important polyketides for prospective SAR studies.

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