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The Synthesis of an Exhaustively Stereodiversified Library of *cis*-1,5 Enediols by Silyl-Tethered Ring-Closing Metathesis

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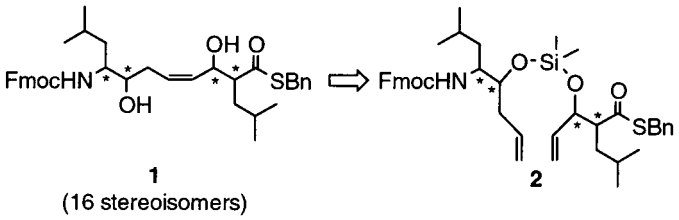
ABSTRACT



This report describes the parallel synthesis of all 16 stereoisomers of the *cis*-1,5 enediol module 1. Compounds 1 derive from 2 by silicon-tethered ring-closing metathesis. Such libraries of stereodiversified ligands provide a unique approach to ligand discovery that employs exhaustive searching of conformational space.

Diversity-oriented synthesis aims to create arrays of low-molecular-weight organic compounds having different molecular shapes, usually with the goal of discovering novel bioactive substances.[1] With few exceptions, these syntheses have achieved diversity in shape through variation of molecular constitution.[2] A complementary approach is to vary the stereochemistry of compounds having the same constitution.[3] Whereas the former approach probes functional group space by varying moieties presented from a common scaffold, the latter explores conformational space through geometric variation of the ligand scaffold. Stereochemistry can profoundly affect the strength and specificity of receptor−ligand interactions and may also influence pharmacologic properties such as biodistribution, metabolism, and toxicity.[4,5]

The synthesis of exhaustively stereodiversified libraries presents a challenge in that it requires the implementation of reactions that are highly stereoselective, together with reactions that are highly tolerant of stereochemical context. Indeed, few examples of exhaustively stereodiversified ligand libraries have been reported, the first being the synthesis of all 32 stereoisomers of a polyketide having 5 stereogenic centers.[6] We recently reported the synthesis of all 16 stereoisomers of the *cis*-1,4-enediol **5** (Figure 1).[5] These compounds are of interest because the dense packing of sp^3

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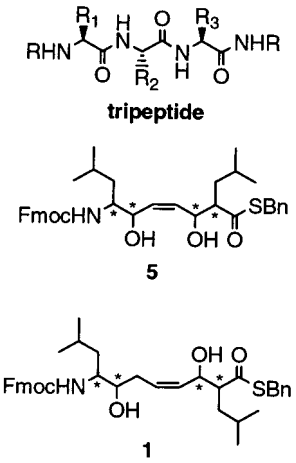


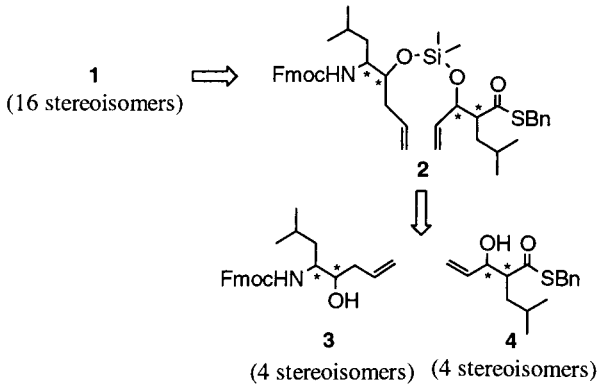
Figure 1.

stereocenters flanking the *cis* olefin results in strong torsional constraints; the interactions of these ligands with receptors are thus governed by acyclic stereocontrol. Moreover, the molecules possess functionally differentiated termini that allow for further elaboration into libraries having both stereochemical and constitutional diversification. The synthesis of stereoisomers **5** employed a convergent, stereocontrolled approach based on chiral auxiliary-directed aldol reactions and silyl-tethered ring-closing metathesis (RCM).[7]

Exhaustive searching of stereochemical space might be an especially apt strategy for the discovery of ligands that bind peptide receptors. Whereas compounds **5** possess one fewer atom in the main chain than a corresponding tripeptide, the main chain of system **1** is isoatomic with a tripeptide (Figure 1). Although both **1** and **5** are conformationally constrained, **1** has greater flexibility owing to the presence of an unsubstituted allylic position. This increased flexibility may raise the entropic cost of binding a receptor; however, it may also allow **1** to access biologically active conformations not available to **5**. Moreover, the hydroxyl groups of **1** are chemically differentiated (allylic/homoallylic), unlike those of **5** (allylic/allylic), thus raising the prospect for selective hydroxyl-directed derivatization of the compounds **1**. Herein we report the stereocontrolled, spacially separated synthesis of all 16 stereoisomers of **1**.

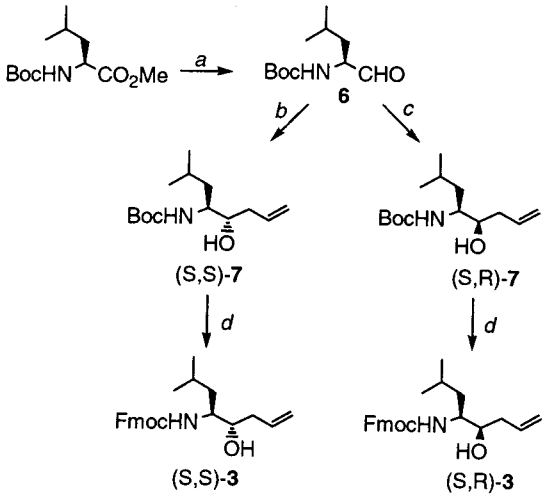
Retrosynthetically, **1** derives through RCM from **2**, which is assembled by silyl-tethering of monomers **3** and **4** (Scheme 1). The four stereoisomers of **3** were prepared through Brown allylation chemistry, utilizing a chiral allylborane to achieve reagent-controlled stereoselective allylation (Scheme 2).[8] Thus, Boc-L-Leu-OMe was reduced to aldehyde (*S*)-**6** using DIBAL-H and then allylated with (+)-Ipc_2B-allyl to generate (*S*,*S*)-**7** (92:8 ratio of diastereomers) or with (−)-Ipc_2B-allyl to generate (*S*,*R*)-**7** (93:7 ratio of diastereomers). The Boc

Scheme 1. Retrosynthetic Analysis of **1**



protecting group was exchanged for an Fmoc group to give (*S*,*R*)-**3** and (*S*,*S*)-**3**. The procedure was repeated with the Boc-D-Leu-OMe to give (*R*,*S*)-**3** and (*R*,*R*)-**3**.

Scheme 2[a]



[a] Key: (*a*) DIBAL-H, toluene, −78 °C; (*b*) (+)-Ipc_2B-allyl, Et_2O, 60% 2 steps; (*c*) (−)-Ipc_2B-allyl, Et_2O, 61% 2 steps; (*d*) i. TFA, CH_2Cl_2, ii. Fmoc-NHS, K_2CO_3, dioxane, H_2O, 70%.

The four stereoisomers of **4** were synthesized according to a published procedure.[5] (*R*,*S*)- and (*S*,*R*)-**4** were derived from a chiral auxiliary-directed Evans aldol reaction,[9] and (*R*,*R*)- and (*S*,*S*)-**4** were synthesized by a chiral auxiliary-directed Masamune aldol reaction.[10]

In preparation for RCM, each stereoisomer of **4** was covalently tethered to each stereoisomer of **3** through a dimethylsilyl linker to generate the 16 stereoisomers of **2** (Scheme 3). Compounds **4** were monosilylated with 20 molar equiv of Cl_2SiMe_2; the excess silane was removed in vacuo, and then 1.2 molar equiv of **3** was added. The yield of the

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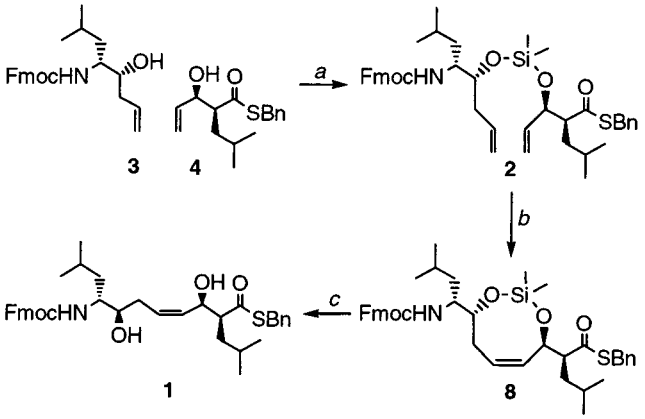
Scheme 3[a]



[a] Key: (*a*) **4**, Me_2SiCl_2, pyridine, then **3**, pyridine, 55%; (*b*) $Cl_2(PCy_3)(IMes)Ru{=}CHPh$, toluene, 95 °C, 89%; (*c*) HF/pyridine, THF, 0 °C, 87%.

silyl-tethered product was markedly dependent upon the stereochemistry of **4**, with (*R*,*R*)- and (*S*,*S*)-**4** providing 69−100% yield of the tethered product, vs 34−64% yield using (*R*,*S*)- and (*S*,*R*)-**4**.

The RCM of **2** to form **8** involves the formation of an eight-membered ring. The RCM of medium-sized rings typically requires a certain amount of preorganization into a quasicyclic structure.[11] Consequently, we were concerned that stereodiversity in RCM substrates **2** might give rise to variability in cyclization, due to effects on the degree of preorganization. Indeed, in the only other published RCM of an eight-membered silyl-tethered heterocycle,[12] the reaction was found to be highly diastereoselective when performed with the prototypical Grubbs metathesis catalyst[13] $Cl_2(PCy_3)_2Ru{=}CHPh$; however, this diastereoselectivity could be overcome by using the more active catalyst $Cl_2(PCy_3)(DHIMes)Ru{=}CHPh$.[14] In a similar manner, the RCM of **2** with 5−10 mol % of $Cl_2(PCy_3)(IMes)Ru{=}CHPh$[15] in toluene at 95 °C for 1 h gave excellent yields (78−94%, Table 1) of the stereoisomeric cyclization products **8**.

Table 1. Stereochemical Dependence of RCM of **2** To Form **8**[a]

config (N·C)	yield (%)	catalyst (mol %)	ring substitution
RRSR	85	5	*cis*
RRSS	94	5	*cis*
RSRR	86	5	*cis*
RSRS	84	5	*cis*
RRRS	89	10	*trans*
RRRR	86	10	*trans*
RSSS	88	10	*trans*
RSSR	78	10	*trans*

[a] Reactions were carried out under argon in toluene at 95 °C for 1 h.

Although RCM to generate the products **8** having the ring substituents oriented *cis* required less catalyst than that for *trans*-substituted **8** (5% compared to 10%), the isolated yields of the products were comparable. In all cases, elevated reaction temperatures and the highly active second-generation ruthenium catalyst were necessary to achieve these uniform results. For example, (*R*,*S*,*R*,*S*)-**2** and (*R*,*R*,*R*,*S*)-**2** underwent RCM at 95 °C in 84% and 89% yields, respectively, as compared with 79% and 67% at 70 °C. On the other hand, treatment of Boc-protected versions of (*R*,*S*,*R*,*S*)-**2** and (*R*,*R*,*R*,*S*)-**2** with 75 mol % of $Cl_2(PCy3)_2Ru{=}CHPh$ at 40 °C in CH_2Cl_2/THF for 42 h gave only 64% of (*R*,*S*,*R*,*S*)-**8** and no observable (*R*,*R*,*R*,*S*)-**8**.

To complete the synthesis, the 16 stereoisomers of **8** were deprotected with HF/pyridine in THF to give the 16 stereoisomers of **1** in 51−91% yield. Over the three steps shown in Scheme 3, the yields for the products ranged from 18 to 78%. In yet to be published work, the entire panel of stereoisomers has been found to undergo efficient incorporation into chimeric peptides, which are suitable for use in biologic screening (B.A.H. and G.L.V, unpublished results).

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Supporting Information Available: Experimental details and characterization data regarding the preparation of all synthetic intermediates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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