Asymmetric Synthesis

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Isoxazole-Directed Pinacol Rearrangement: Stereocontrolled Approach to Angular Stereogenic Centers**

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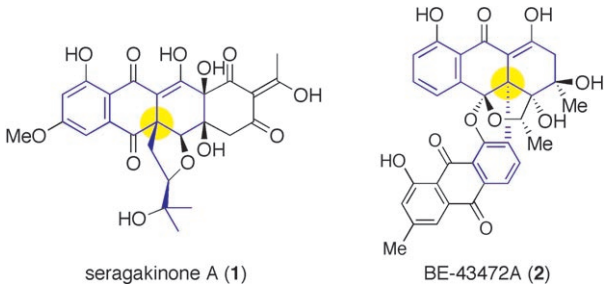
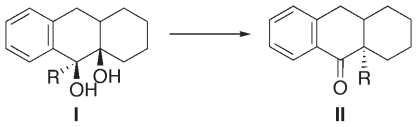
In our synthetic studies towards some polyketide-derived natural products, including seragakinone A (**1**)[1] and the antibiotic BE-43472A (**2**),[2] we required a general and effective method for establishing quaternary stereogenic centers at the angular position in these polycyclic compounds (Scheme 1). With the recognition that conventional strategies



Scheme 1. Polyketide-derived polycyclic natural products with angular substitution.

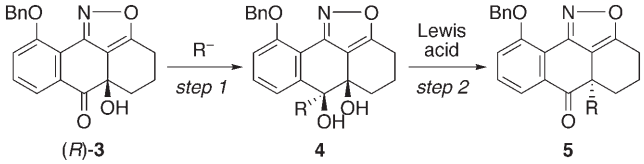
for the stereocontrolled construction of quaternary carbon centers, for example, enolate alkylation and nucleophilic displacement reactions,[3] would not provide a general solution to this problem, we envisaged that an indirect but efficient route to the angularly substituted ketone **II** would be available by the pinacol rearrangement of the tricyclic diol **I** (Scheme 2).[4]

For such a scenario to be feasible, however, two critical requirements must be fulfilled: 1) The diol **I** needs to be readily available in a stereodefined form, and 2) the 1,2-shift must occur in a regioselective and stereospecific manner. The latter criterion is challenging, because the two hydroxy groups in **I** are both tertiary and therefore equally susceptible to acid-activated departure. Even if selective activation of the angular hydroxy group is possible, the relative migratory aptitudes of the pendant groups may induce further complications.



Scheme 2. Pinacol-rearrangement approach for installing angular substituents.

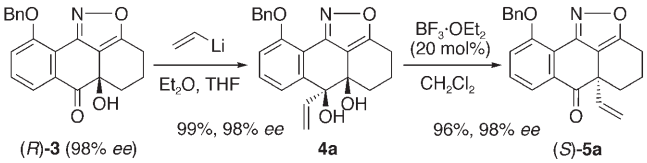
We now report the successful implementation of this strategy in the form of an isoxazole-directed pinacol rearrangement for the stereoselective introduction of angular substituents in polycyclic systems. Scheme 3 illustrates the



Scheme 3. Two-step installation of angular substituents. Bn = benzyl.

two-step process, which has two crucial attributes. First, the *cis* diol **4** is readily accessible in stereocontrolled manner by the addition of a nucleophile (R^-) to the readily prepared chiral, nonracemic ketol **3**.[5,6] Second, the pinacol rearrangement, **4**→**5**, proceeds in a regioselective and stereospecific manner as a result of the excellent, and underappreciated, α-cation-stabilizing ability of an isoxazole.

Pleasingly, the addition of carbon nucleophiles to ketol **3** occurred in a highly *cis*-selective manner under various conditions. For example, the slow addition of a solution in THF of ketol (*R*)-**3** (98% *ee*) to a solution of vinyllithium[7] in Et_2O at −78 °C gave the *cis* diol **4a** after 5 min as a single product in 99% yield (Scheme 4). Enantiomeric purity was preserved during this process, as evidenced by HPLC analysis on a chiral stationary phase;[8] diol **4a** was obtained with 98% *ee*.



Scheme 4. Installation of an angular vinyl group.

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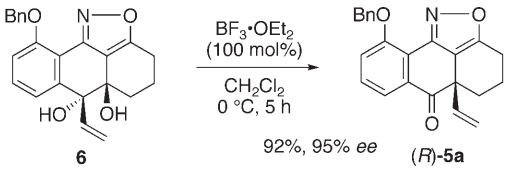
We next examined the viability of the second step, the pinacol rearrangement of the stereodefined model diol **4a**. We regarded this model system as a challenging test case, because undesired carbocation formation at the benzylic position should be facilitated by the presence of a vinyl group. It was a pleasant surprise to find that only the desired reaction occurred under a variety of conditions. For example, when diol **4a** was treated with $BF_3{\cdot}OEt_2$ (20 mol%; CH_2Cl_2, 0°C, 3 h), a smooth 1,2-shift of the vinyl group occurred to give the ketone **5a** with an angular vinyl group in 96% yield.[9]

Two features of this reaction are notable: 1) The desired 1,2-shift of the vinyl group occurred exclusively, and 2) the 1,2-shift was stereospecific; the vinyl group shifted in a suprafacial manner to give the ketone with the *S* configuration.[10] No loss of enantiopurity was observed during this migration process, as evidenced by the HPLC analysis of **5a** on a chiral stationary phase (98% *ee*).[8]

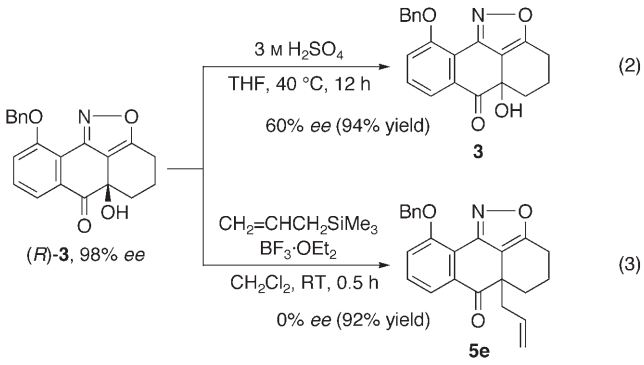
We initially reasoned that this facile and stereospecific 1,2-shift was a result of the ideal stereoelectronic relationship in the starting diol **4a**, in which the acid-promoted departure of the angular hydroxy group is assisted by the antiperiplanar vinyl group to allow smooth progression to the concerted 1,2-shift.[11] However, it turned out that, albeit helpful, such anchimeric assistance is not essential; the isomeric diol **6** also showed a preference for the departure of the angular hydroxy group [Eq. (1)].[12] Upon exposure to $BF_3{\cdot}OEt_2$ (1 equiv; CH_2Cl_2, 0°C, 5 h), the *trans* diol **6** also underwent a slow, but steady, 1,2-shift of the vinyl group. Importantly, the opposite enantiomer (*R*)-**5a** was obtained (compare with Scheme 4), which is highly intriguing in view of the fact that the stereocenter with the hydroxy leaving group has the same configuration in diols **4a** and **6**.



(1)

These unexpected results suggested that the origin of the regioselective 1,2-shift is an excellent ability of isoxazoles to facilitate the formation of an adjacent carbenium ion. This postulate was supported by the observation that the chiral, nonracemic ketol (*R*)-**3** underwent facile racemization upon exposure to a protic acid [Eq. (2)]: a remarkable finding given that cation formation at the α position to a carbonyl group is a disfavored process.[13] Furthermore, the treatment of (*R*)-**3** with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$ afforded smoothly the allylated product **5e** in racemic form [Eq. (3)]. These results are consistent with the intermediacy of a well-developed cationic species adjacent to an isoxazole.

The overall process is summarized as Scheme 5, which takes all these data into account. Two cationic species, **A** and **B**, can potentially be generated from the *cis* diol. Cation **A** is a productive species, which leads to a suprafacial 1,2-shift to give product **C**. Cation **B**, on the other hand, is an epimerizing species capable of supplying the *trans* diol, which could react to produce the enantiomeric product, *ent*-**C**, via the enantiomeric cation *ent*-**A**. The experimentally observed stereospecific 1,2-shift (Scheme 5; R = vinyl) could be explained by the excellent migratory aptitude of a vinyl group,[14] which suppresses the intervention of the stereomutating process.

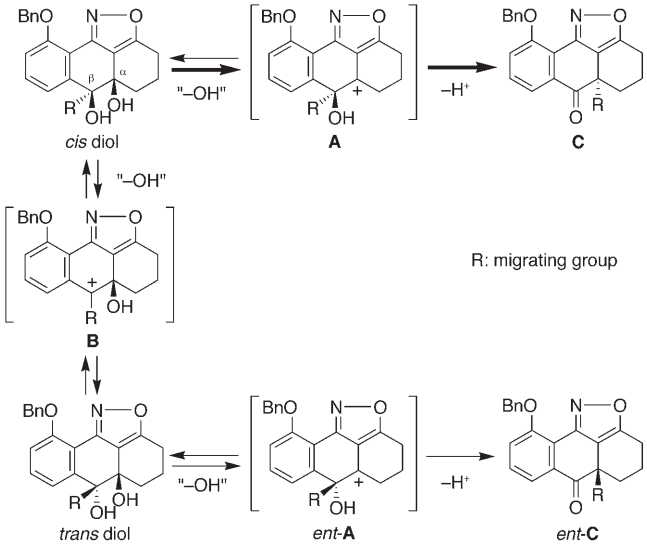


(2)

(3)

Despite such mechanistic considerations, this two-step process proved to be applicable to a variety of migrating groups to provide efficient, stereospecific access to the corresponding angularly substituted polycyclic structures (Table 1). In all cases listed, the installation of the migrating group, R, gave a single *cis* diol **4b–f**. The standard conditions (20 mol% of $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0°C) were effective for the 1,2-shift of good migrating groups, including an aromatic, a heteroaromatic,[14a,15] and an allyl group, to establish the quaternary stereogenic center at the angular position.

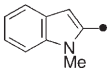
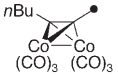
A single exception was the 1,2-shift of a 1-alkynyl group (Table 1, entry 5): The product **5f** was obtained in partially racemized form (71% *ee*), as further supporting evidence for



Scheme 5. Proposed mechanistic scheme for the pinacol rearrangement.

our mechanistic postulate. A 1-alkynyl group has a poor migratory aptitude[11,16] but a good cation-stabilizing ability. Thus, there is time for the stereochemical mutation to occur before the slow 1,2-shift proceeds. We were pleased to find an indirect but effective way of promoting the alkynyl shift by converting **4f** into the corresponding $[Co_2(CO)_6]$ complex **4g** (Table 1, entry 6).[17] Although a slight decrease in the

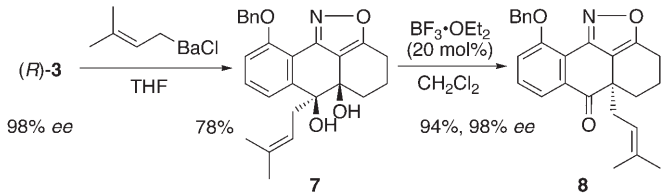
Table 1: Substrate scope in the pinacol rearrangement to install angular stereogenic centers.[a,b]

Entry	R[c]	Yield [%] (step 1)	*T* [°C]	*t* [h]	Yield [%] (step 2)	*ee* [%]
1		89 (**4b**)	0	1	92 (**5b**)	98
2		94 (**4c**)	0	3	90 (**5c**)	98
3		87 (**4d**)	0	1.5	96 (**5d**)	98
4		90 (**4e**)	0	2	95 (**5e**)	98
5		98 (**4f**)	25	9	86[d] (**5f**)	71
6		– (**4g**)	0	5	82[d,e] (**5f**)	96

[a] Step 1: R groups were installed by adding R–Li or R–MgX (2.5–3.0 equiv) to (*R*)-**3** (98% *ee*). [b] Step 2: Unless otherwise noted, the reaction was performed with $BF_3{\cdot}OEt_2$ (20 mol%) in CH_2Cl_2 at the temperature indicated. [c] The dot represents the position of connectivity. [d] A stoichiometric amount of $BF_3{\cdot}OEt_2$ was used. [e] Overall yield for 3 steps: complexation, rearrangement, and decomplexation; see the Supporting Information.

ee value was noted, the angularly alkynylated product **5f** (96% *ee*) was obtained in high yield (82% over three steps) by the facile 1,2-shift of the complexed alkynyl group followed by decomplexation.

The excellent migratory behavior of an allyl group (Table 1, entry 4) encouraged us to exploit this process in the context of the synthesis of isoprenoid-containing natural products, such as **1**. Pleasingly, a prenyl group could be introduced stereo- and regioselectively at the angular position by the treatment of (*R*)-**3** with a prenylbarium reagent[18] followed by the $BF_3{\cdot}OEt_2$-catalyzed rearrangement (Scheme 6).



Scheme 6. Selective installation of a prenyl group.

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[8] The *ee* values were determined by HPLC analysis with a Chiralpak AD-H column (see Supporting Information).

[9] The following chemical yields were recorded when other (Lewis) acids were used: Et_2AlCl: 76%, $TiCl_4$: 75%, $Sc(OTf)_3$: 91%, trifluoroacetic acid (TFA): 77%, triflic acid (TfOH): 92%.

[10] The *S* absolute configuration of ketone **5a** was determined by single-crystal X-ray analysis of the (*S*)-camphanate derivative, which was obtained by the reduction of **5a** ($NaBH_4$, THF, MeOH, 0°C) to give the *cis* diol as a single product followed by esterification of the secondary alcohol with (*S*)-camphanic chloride (DMAP, CH_2Cl_2, 0°C) (see Supporting Information).

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