Natural Products

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Parallel Kinetic Resolution Approach to the Cyathane and Cyanthiwigin Diterpenes Using a Cyclopropanation/Cope Rearrangement**

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Traditional ("simple") kinetic resolution (KR) enables the separation of an equal mixture of enantiomers (e.g. **E**(*R*) and **E**(*S*), Figure 1) based on a difference in the reaction rate of each enantiomer with a single chiral reagent (i.e. $k_{\mathbf{E}(R)} \neq k_{\mathbf{E}(S)}$).[1] In the ideal case, one enantiomer (e.g. **E**(*R*)) undergoes complete conversion into a product (**P**(*R*)), whereas the other enantiomer (**E**(*S*)) remains unchanged. In the best case scenario, both the product (**P**(*R*)) and the unchanged enantiomer (**E**(*S*)) are obtained enantiomerically pure.[2] An alternative to KR, which circumvents many of its challenges (e.g. concentration effects and requisite high selectivity factors)[3] is parallel kinetic resolution (PKR; see Figure 1).[4] In PKR, both enantiomers react efficiently with a chiral reagent, but are converted into products that are not enantiomers.

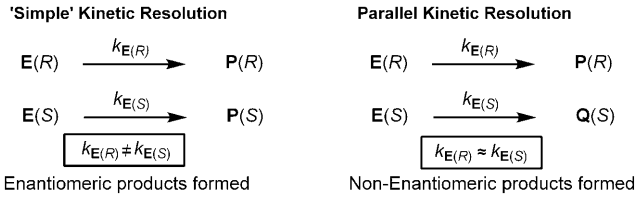
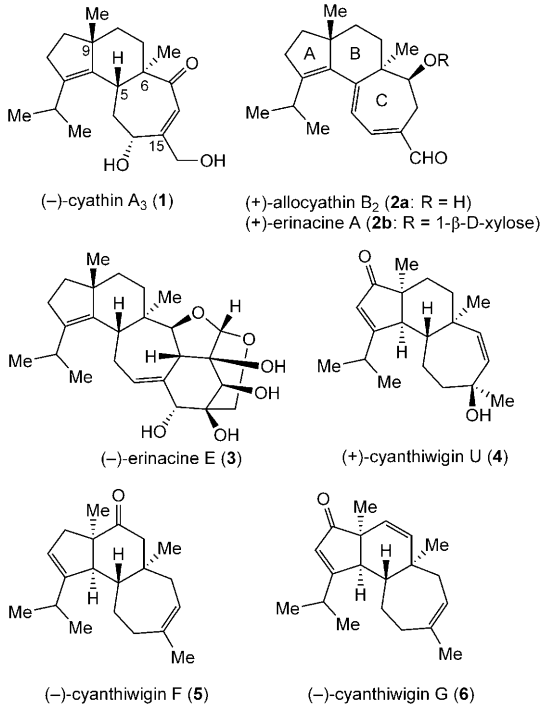


Figure 1. Representation of "simple" kinetic resolution and parallel kinetic resolution.

Even in an ideal kinetic resolution (simple or parallel), only one of the enantiomers of the starting material (or its corresponding product) is usually desired. As a result, the other enantiomeric starting material (or product) must be discarded or recycled for another round of resolution. Herein, we report a rare example of stereodivergent PKR[5] whereby a 50:50 mixture of enantiomers is resolved into enantioenriched diastereomers, each of which is the naturally occurring antipode of an intermediate en route to the cyathane and cyanthiwigin diterpenes.

The cyathane and cyanthiwigin diterpenes are a growing family of structurally related natural products possessing a [5-6-7] tricyclic core (Scheme 1).[6] These compounds have been isolated from both terrestrial as well as marine sources.[7] The tricyclic core of these compounds is found at various stages of oxidation, which poses a significant challenge in defining a general strategy to access all the natural products in this class. However, this variety in oxidation levels leads to an exciting array of bioactivity including nerve-growth factor stimulation (with potential implications for combating neurodegenerative disorders),[8] anti-HIV activity, cytotoxicity, and inhibition of *Mycobacterium tuberculosis*.[6,7b,e]



Scheme 1. Selected cyathane and cyanthiwigin natural products.

A major difference among these diterpenoids is the stereochemical relationship between the two quaternary methyl groups at C6 and C9 (see **1**), which are either disposed *anti* (cyathanes) or *syn* (cyanthiwigins). An additional difference is in the stereochemical relationship of the hydrogen

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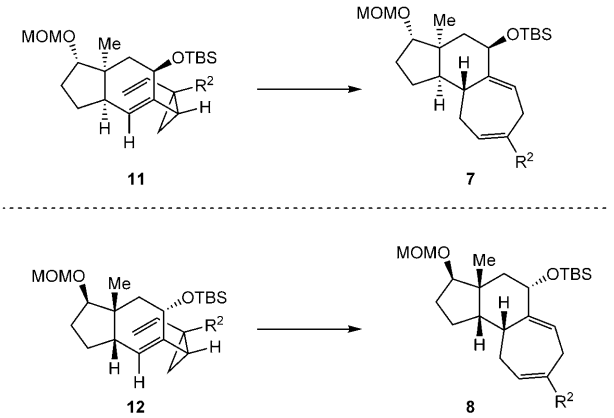
atom at C5 relative to the methyl group at C9, which is *syn* in the cyathane core and *anti* in the cyanthiwigin core. These structural variations must be taken into account when designing a unified synthesis that aims to access all these natural products.

Interest in these compounds has resulted in several total syntheses of the cyathane diterpenes,[9] the first of which were of (±)-allocyathin B_2 (**2a**) and (+)-erinacine A (**2b**) by Snider et al.[9a,b] In addition to the existing total syntheses, a number of strategies have been adopted for the synthesis of the seven-membered ring to complete the tricyclic core of these compounds.[10] In contrast, the related cyanthiwigin diterpenes have received comparatively little attention. Only three reports of total syntheses of the [5-6-7] tricyclic congeners of this family have appeared.[11] In 2005, Pfeiffer and Phillips reported a total synthesis of (+)-cyanthiwigin U (**4**) by using an innovative two-directional ring-opening/ring-closing metathesis (ROM/RCM) strategy.[12] Unfortunately, this strategy has not been amenable to the synthesis of other cyanthiwigins such as cyanthiwigin F or G (**5** or **6**) because the requisite substrates for the analogous ROM/RCM, which would possess a functionalized B ring, have been unattainable. This challenge of B ring functionalization has been partly addressed by an elegant synthesis of (−)-cyanthiwigin F (**5**) by Enquist and Stoltz.[13]

In considering a unified synthesis of the cyathane and cyanthiwigin diterpenes, we concluded that the most challenging aspects are: 1) stereoselective installation of the *syn*-1,4 (or *anti*-1,4) quaternary methyl groups at C6 and C9; 2) control of the stereocenter at C5; and 3) the introduction of varying degrees of oxygenation or unsaturation on the tricyclic framework (especially the B ring). Herein, we present our strategy to access these compounds that addresses the latter two of these challenges by taking advantage of PKR (Scheme 2).

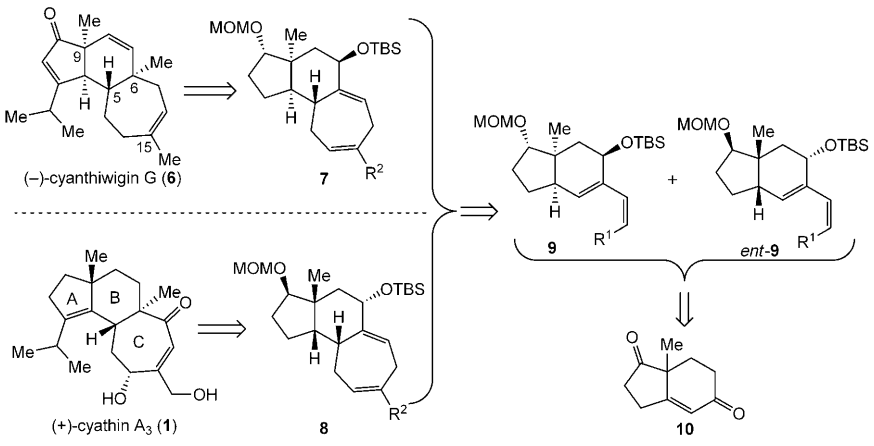
As an example of our approach, (−)-cyanthiwigin G or (+)-cyathin A_3 would arise from enantioenriched tricycles **7** or **8**, respectively (Scheme 2). We envisioned that both tricycles could be generated from a functionalized racemic diene (**9** and *ent*-**9**). In this scenario, enantiomer **9** would lead to **7**, whereas *ent*-**9** would yield **8** through PKR. The racemic diene could in turn be obtained from racemic Hajos–Parrish ketone (**10**).[14] Key to this strategy is the ability to elaborate the racemic mixture of dienes (**9** and *ent*-**9**) to enantioenriched divinylcyclopropanes **11** or **12** (Scheme 3) using a single chiral, non-racemic cyclopropanating agent. The intermediate divinylcyclopropanes were expected to undergo facile rearrangement to cycloheptadienes **7** or **8**, respectively.[15]



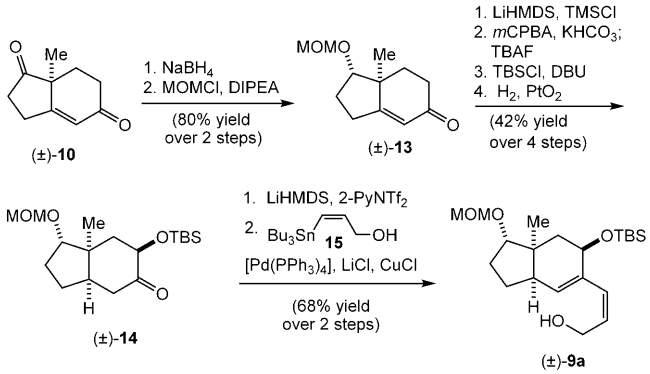
Scheme 3. Divinylcyclopropane rearrangements.

The success of our PKR strategy rested on the ability to achieve 1) indiscriminate cyclopropanation of the 50:50 mixture of dienes **9** and *ent*-**9** at comparable rates with a single chiral, enantiopure reagent, and 2) straightforward separation of the resulting diastereomers (i.e. **7** and **8**). We decided to first investigate these factors with simple model system **9a**, which was prepared from readily available racemic Hajos–Parrish ketone (Scheme 4).[16] Following literature precedent,[17] chemo- and diastereoselective reduction of the ketone functional group in **10** and MOM protection of the resulting hydroxy group afforded enone **13** (>20:1 d.r.). Functionalization of the B ring was accomplished through a sequence developed by Rubottom et al. (5:1 d.r.).[18] Silyl protection of the hydroxy group and diastereoselective hydrogenation with Adams' catalyst afforded α-silyloxy ketone **14** in 42% yield over the four steps. Kinetic enolization and triflation of ketone **14**, and subsequent coupling with vinyl stannane **15**[19] under the Corey-modified Stille conditions[20] gave dienol **9a** in 68% yield over two steps.

To determine the inherent substrate diastereoselectivity in the cyclopropanation of the model diene **9a**, we employed Simmons–Smith conditions[21] and were able to regioselectively install the cyclopropane unit on the alkene proximal to the hydroxy group (Scheme 5). This yielded a read-



Scheme 2. Retrosynthetic strategy based on parallel kinetic resolution. MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl.



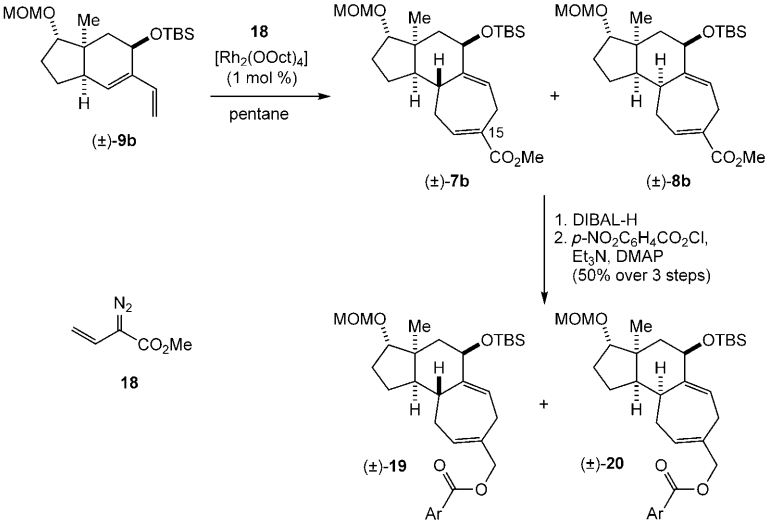
Scheme 4. Synthesis of dienol **9a**. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIPEA = *N*,*N*-diisopropylethylamine, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, *m*CPBA = *meta*-chloroperoxybenzoic acid, Py = pyridine, TBAF = tetra-*n*-butylammonium fluoride, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

ily separable 1:1 diastereomeric ratio of cyclopropanes **16** and **17**,[22] consistent with a lack of substrate control from the resident stereocenters in dienol **9a** under the reaction conditions.

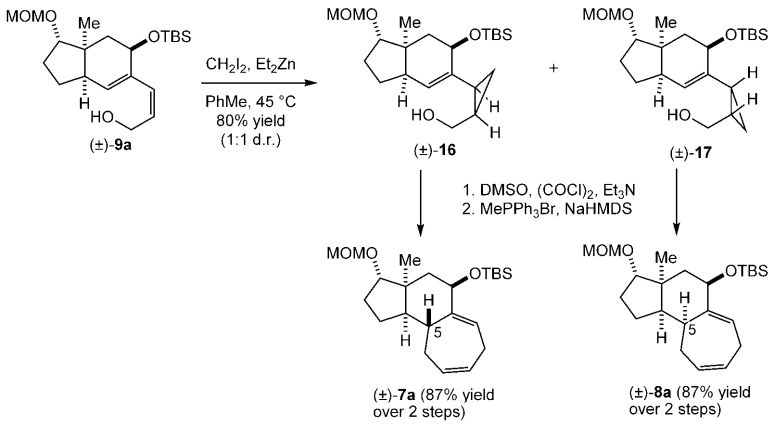
Either cyclopropane (**16** or **17**) was readily converted into the corresponding tricyclic cycloheptadiene required for the total synthesis of the cyanthiwigin or cyathane diterpenes (**7a** and **8a**, respectively).[23] Specifically, this was achieved by Swern oxidation of the primary hydroxy group of **16** or **17**, and subsequent methenylation of the crude aldehyde to afford the tricyclic product in 87% overall yield for each diastereomer. Presumably, the [3,3]-sigmatropic rearrangement occurs rapidly once the methylene group is installed. Importantly, the configuration of the cyclopropane ring determines the configuration about the C5 center, as the divinylcyclopropane rearrangement proceeds stereospecifically.[24]

On the basis of these model studies, we initiated an exploration of parallel kinetic resolution of racemic dienes by using the Davies vinyldiazoacetate method for asymmetric cyclopropanation.[25,26] In this streamlined strategy, the cyclopropanation and Cope rearrangement steps are coupled through the use of vinyldiazoacetate **18**[27] (Scheme 6). This approach has the added benefit of installing an ester group at C15, which may be converted into the appropriate functionality (e.g. a methylene hydroxy group for the cyathane diterpenes) in subsequent steps (see **7b** to **19**). We initiated these studies with racemic diene **9b**, which was prepared from **14** through vinyl triflate formation and subsequent Stille coupling with vinyltributyltin.[28]

Using (±)-**9b**, both diastereomers of the tricycle (i.e. **7b** and **8b**) were obtained in a 1:1 ratio using rhodium(II) octanoate to catalyze the diazo decomposition (Scheme 6 and Table 1, entry 1).[29,30] Consistent with our earlier observations (Scheme 5), there appears to be minimal substrate stereocontrol in the cyclopropanation step. Owing to the relative instability of **7b** and **8b**, these compounds were purified and characterized after reduction of the ester group and derivatization of the resulting hydroxy group as the *p*-nitrobenzoate (see **19** and **20**; obtained in 50% combined yield over 3 steps).



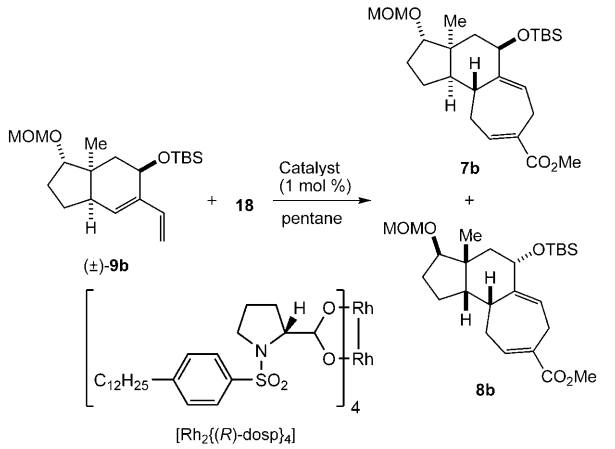
Scheme 6. A racemic synthesis of the cycloheptadiene diastereomers. DIBAL-H = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine.



Scheme 5. Divergent Simmons–Smith cyclopropanation. DMSO = dimethyl sulfoxide.

Under reaction conditions where ideal PKR could be realized, cyclopropanation of racemic **9b** with a chiral non-racemic catalyst should lead to divergent paths for each enantiomer to yield enantioenriched diastereomers **7b** and **8b**. In reality, the facial selectivity of the cyclopropanation catalyst is not perfect, and we observe some leakage (i.e. approach of the catalyst from the less favorable face of the diene; vide infra). This is reflected in the enantiomeric ratios of **7b** and **8b** (Scheme 7),[31] which are formed as a 1:1 mixture of diastereomers.[32]

Specifically, cyclopropanation of (±)-**9b** using Davies' dirhodium tetraprolinate catalysts ([Rh_2{(*R*)-dosp}$_4$] and [Rh_2{(*S*)-dosp}$_4$]) afforded **7b** and **8b** each in ≥85:15 e.r. as outlined in Scheme 7 (Table 1, entries 2 and 3). Importantly,



Scheme 7. Parallel kinetic resolutions using vinyldiazoacetate cyclopropanations. dosp = *N*-[(4-dodecylphenyl)sulfonyl] prolinate.

the enantiomeric ratio could be reversed for each cycloheptadiene depending on the tetraprolinate catalyst that was employed (compare Table 1, entries 2 and 3). These studies illustrate that starting from racemic **9b**, it is possible to effect a resolution en route to the tricyclic cores of the cyanthiwigin and the cyathane diterpenes, each enriched in the naturally occurring enantiomer.

Given the complexity of **9b**, which contains multiple resident stereocenters, the observed selectivity of the PKR step was highly encouraging. To gain more insight into the stereodivergent cyclopropanation step, we conducted the analogous cycloheptadiene-forming steps with enantioenriched dienes (+)-**9b** and (−)-**9b** (Scheme 8). The facial selectivity of the cyclopropanation step becomes more transparent with these substrates. For example, (+)-**9b** should afford only (−)-**7b** with the [Rh_2{(*R*)-dosp}$_4$] catalyst [Eq. (1)] if the facial discrimination of the cyclopropanation were perfect. However, the modest selectivity led to a 7:1 ratio of (−)-**7b** to (+)-**8b**. Similar selectivities were observed when starting with (−)-**9b** as the substrate as well as using [Rh_2{(*S*)-dosp}$_4$] as the catalyst. Optimization of the stereoselectivity of the cyclopropanation, which is currently ongoing, should enable us to target a single, highly enantioenriched diterpene by starting from either (+)-**9b** or (−)-**9b**.

In summary, we have developed a unified strategy to access the enantioenriched tricyclic core of the cyathane and cyanthiwigin diterpenes using a common racemic diene precursor by taking advantage of parallel kinetic resolution. The key step involves a stereoselective cyclopropanation and subsequent stereospecific divinylcyclopropane rearrangement, which furnishes the stereocenter at C5 on the BC ring junction. Application of this approach to the total synthesis of cyathane and cyanthiwigin natural products are underway.

Table 1: Rh^{II}-catalyzed PKR of diene (±)-**9b**.

Entry	Catalyst	Ratio[a] **7b**/**8b**	e.r.[b] (−)-**7b**/(+)-**7b**	e.r.[b] (+)-**8b**/(−)-**8b**
1[c]	[Rh_2(OOct)$_4$]	1:1	–	–
2	[Rh_2{(*R*)-dosp}$_4$]	1:1	12:88	88:12
3	[Rh_2{(*S*)-dosp}$_4$]	1:1	89:11	15:85

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined on samples of **19** and **20** by HPLC on a Chiralcel OD-H column; eluent: 2.0% 2-propanol in hexanes. [c] On multiple runs there was no enrichment within error (±1.5%). Oct = octonate.

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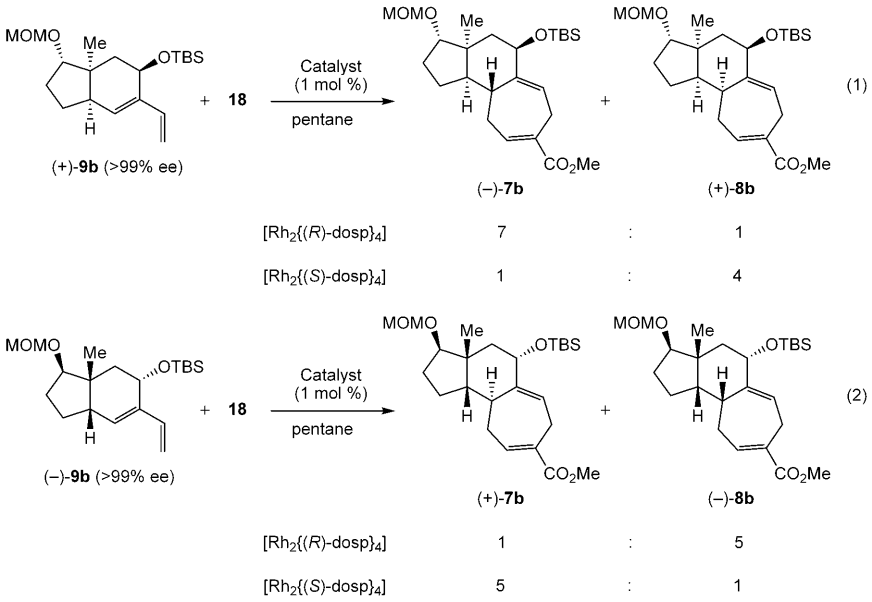

Scheme 8. Using enantioenriched substrates in the vinyldiazoacetate cyclopropanations.

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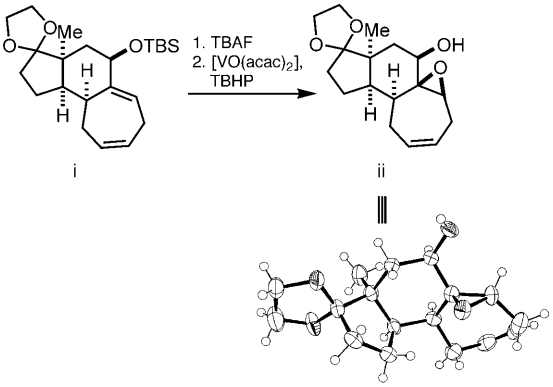
[22] The structures of diastereomers **16** and **17** were inferred on the basis of the corresponding cycloheptadienes (i.e. **7a** and **8a**) that were obtained after the divinylcyclopropane rearrangement.

[23] The structure of the tricycle was confirmed by X-ray crystallography of a derivative (**ii**; TBHP = *tert*-butyl hydroperoxide). CCDC 719055 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.



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[28] See the Supporting Information for details.

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[30] Diene **9b** was determined to be a single diastereomer by HPLC analysis.

[31] Absolute configurations of tricyclic products **7b** and **8b**, obtained from respective parallel kinetic resolutions of (±)-**9b** with $[Rh_2\{(R)\text{-dosp}\}_4]$ and $[Rh_2\{(S)\text{-dosp}\}_4]$ as catalyst, were inferred by comparison to analogous studies with enantioenriched diene substrates (i.e. (+)-**9b** and (−)-**9b**; Scheme 7). For details, see the Supporting Information.

[32] The formation of **7b** and **8b** in 1:1 d.r. points to comparable reaction rates for the enantiomers of **9b**.

