Asymmetric Synthesis Hot Paper

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Bioinspired Total Synthesis of Montanine-Type *Amaryllidaceae* Alkaloids**

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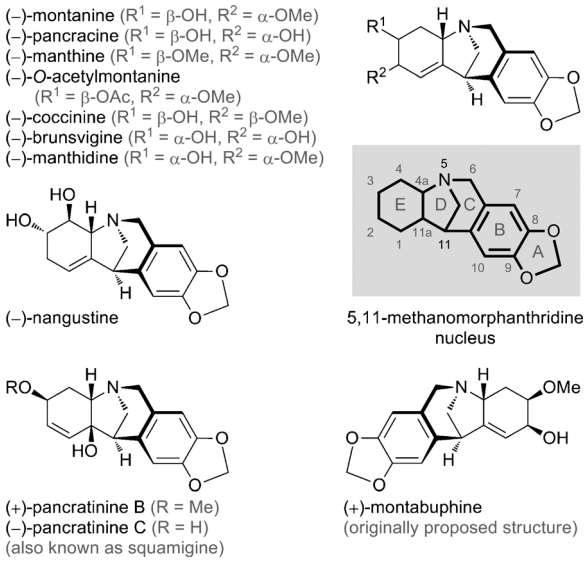
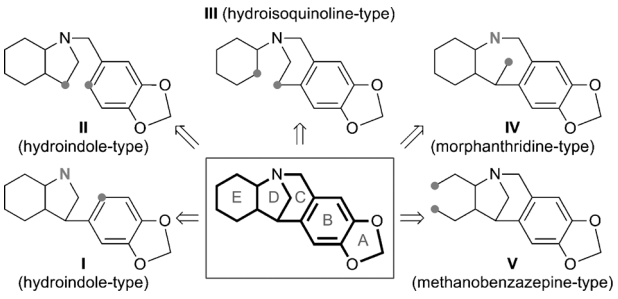
Inspiration from natural products biosynthesis for chemical synthesis has been playing an increasingly crucial role in the discovery and invention of new synthetic strategies and methods:[1] one of the central issues in the field of natural products synthesis. Significantly, the tracking or mimicking of a possible biogenetic pathway to natural molecules could provide a fascinating and meaningful perspective to explore the frontiers of modern organic synthesis with respect to high molecular complexity, structural diversity, and synthetic efficiency. With research interests in the development of biologically inspired approaches to bioactive natural products, we recently selected some montanine-type *Amaryllidaceae* alkaloids[2] (Scheme 1) as the targets for probing such synthesis design in a bioinspired fashion.

The montanine-type alkaloids (Scheme 1) were first isolated by Wildman and co-workers in 1955 from plants of the *Amaryllidaceae* family,[3a] and other congeners were found subsequently in the following decades.[3b–j] Biologically, these alkaloids and derivatives preliminarily exhibited some antimicrobial and psychopharmacological activities.[2e,3h,4] Structurally, naturally occurring montanine-type alkaloids are characterized by a common bridged pentacyclic 5,11-methanomorphanthridine ring system, which constitutes one of twelve main skeleton types of *Amaryllidaceae* alkaloids,[2i] and are distinguished primarily by positional and stereochemical diversity of oxygen-containing substituents in ring E. Clearly, the architectural assembly of the unique 5,11-methanomorphanthridine core in combination with the selective installation of the requisite oxygen-containing functional groups is the most challenging aspect in the enantioselective synthesis of montanine-type alkaloids.



Scheme 1. Representative montanine-type *Amaryllidaceae* alkaloids.

Regarding the chemical synthesis of montanine-type alkaloids, great effort has been made over the past two decades since the pioneering synthetic studies by Overman and Shim[5a] and Hoshino and co-workers[5b] in 1991. In various approaches to the assembly of the 5,11-methanomorphanthridine skeleton, the five types of advanced synthons **I**–**V** (Scheme 2) have been strategically involved,[6–10] and the closure of ring C, D, C/D, or E has constituted the final step in the construction of the polycyclic system. Significantly, the synthetic elaboration of these synthons **I**–**V** has involved the elegant development and application of many novel method-



Scheme 2. Known non-bioinspired strategies for assembling the 5,11-methanomorphanthridine skeleton.

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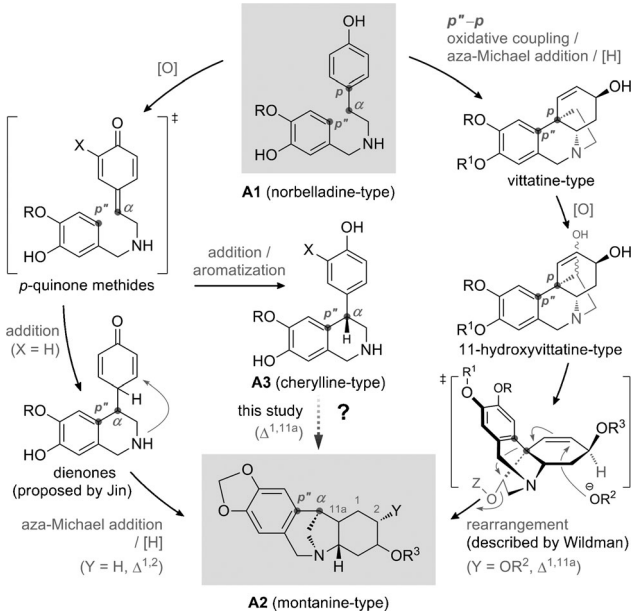
ologies (e.g., an aza-Cope rearrangement/Mannich cyclization,[5a,6a] an allenylsilane imino ene reaction,[9b,c] a [3+2] cycloaddition,[6b,g,10] and a chemoenzymatic approach[6i,k,l]). Despite the substantial progress made in the racemic[5,6c–e,o,7,8,9a,10] and asymmetric[6a,b,f–n,9b,c] synthesis of the montanine-type alkaloids, a general strategy for the effective bioinspired total synthesis of these architecturally unique molecules has not previously been explored.

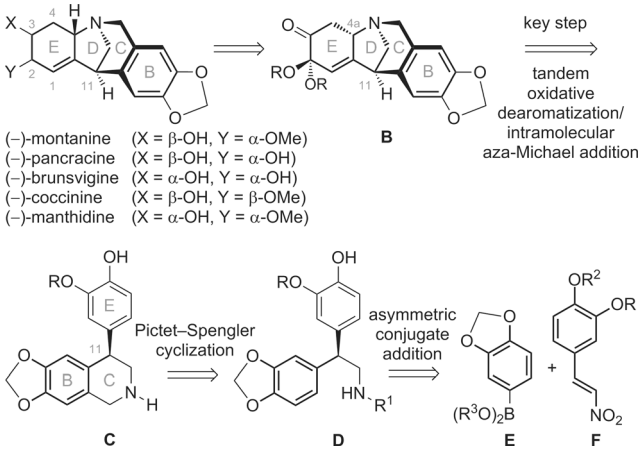
From a biosynthetic point of view, the intriguing biogenesis of the montanine-type *Amaryllidaceae* alkaloids, which can be traced back to norbelladine or its derivatives, has illuminated two distinct biosynthetic proposals for the biochemical conversion of **A1** (norbelladine-type alkloids) into **A2** (montanine-type alkaloids; Scheme 3).[2d,11] One



Scheme 3. Proposed biosynthetic pathways.

pathway (right-hand side) proposed by Wildman and coworkers[11a,c,d] involves a plausible 11-hydroxyvittatine-type precursor and was supported by the serendipitous discovery of the chemical conversion of haemanthamine-type alkaloids into montanine-type derivatives through a stereospecific rearrangement.[3c,4c] Alternatively, a tentative biogenetic route (left-hand side) was deduced by Jin,[2d] who proposed the intermediacy of *p*-quinone methide and dienone species. This state-of-the-art knowledge of the biogenetic origin of the montanine-type alkaloids led us to consider that chemically stable cherylline-type precursors **A3** (Scheme 3) might be involved in the multistep transformation of norbelladine-type intermediates **A1** into montanine-type alkaloids **A2**, and that such intermediates could offer an opportunity to explore a new bioinspired strategy for an expeditious approach to the unique 5,11-methanomorphanthridine ring system.

Retrosynthetic analysis inspired by these considerations (Scheme 4) pointed to the use of an unprecedented tandem oxidative dearomatization/intramolecular aza-Michael addition as a key step[12] in our divergent asymmetric synthesis of five montanine-type alkaloids. Chemically, the diverse oxygen

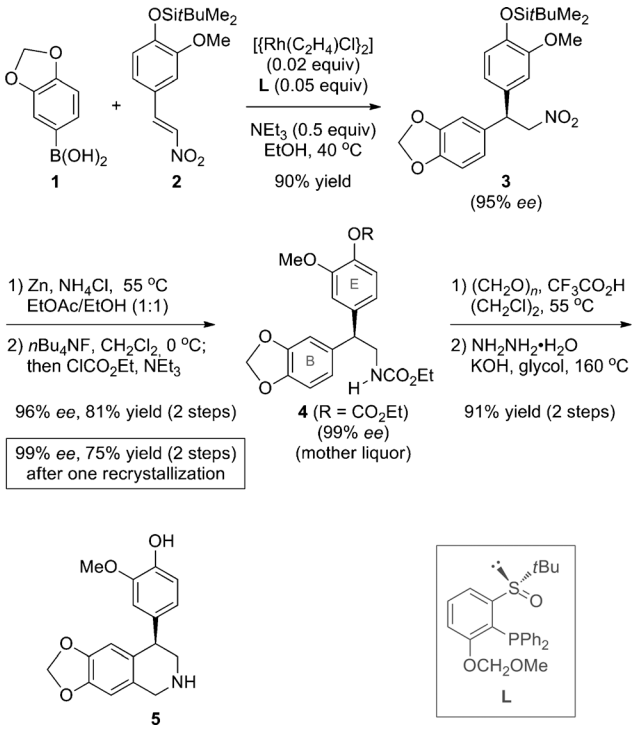


Scheme 4. Retrosynthetic analysis.

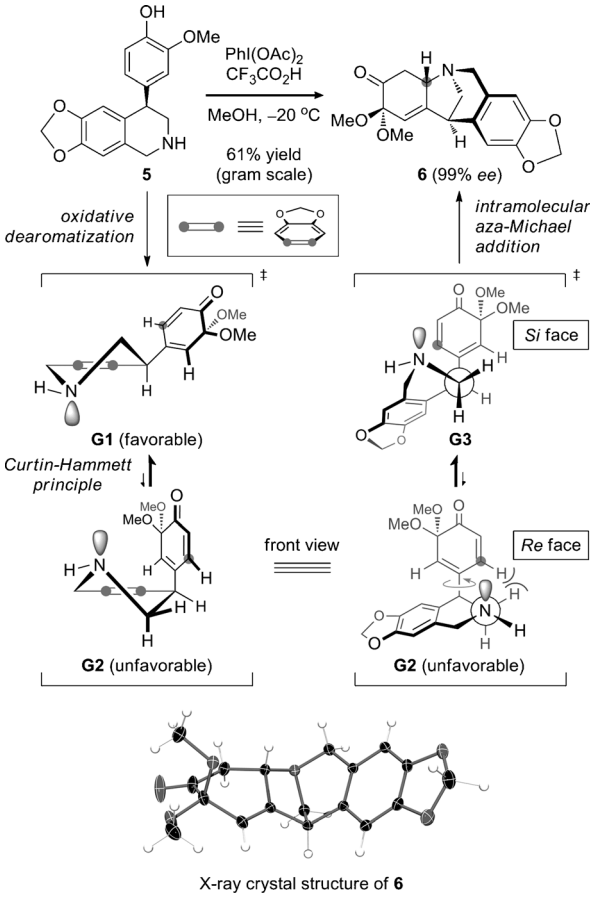
substituents at C2 and C3 in the target alkaloids could be derived by prefunctionalization of the 1,2-diketone monoketal moiety in the common synthon **B**. Strategically, the logical disconnection of the C4a–N bond in ring D of the key montanine-type synthon **B** through a retro-aza-Michael addition would deliver a quinone monoketal intermediate, which could be generated in situ by oxidative phenol dearomatization of the cherylline-type synthon **C**. A selective Pictet–Spengler cyclization of synthon **D** and the asymmetric conjugate addition of organoboron synthon **E** with alkene synthon **F** could be conceived for the formation of the isoquinoline ring C and the crucial C11 diaryl methine stereocenter in the synthon **C**, respectively.

To expediently access the cherylline-type synthon **C** (Scheme 4) for the proposed bioinspired transformation, we began our study with a rhodium-catalyzed asymmetric conjugate addition of aryl boronic acid **1** to nitroalkene **2** with the chiral sulfinylphosphine ligand **L** discovered by Liao and coworkers[13] (Scheme 5). The desired adduct **3** was obtained in 90% yield with 95% *ee*. Reduction of the diaryl nitroethane **3** with Zn powder, followed by fluoride-mediated desilylation and carbamation/esterification, gave the diaryl carbamate **4** (96% *ee*) in 81% yield over two steps. We recrystallized **4** to further enhance its enantiomeric purity. Gratifyingly, the enantiomeric purity of the mother liquor was readily enriched through heterochiral crystallization[14] to afford **4** in 75% overall yield with 99% *ee* after separation of the solid racemate by filtration. Next, following the highly site-selective assembly of a methylene unit on ring B of **4** by a regioselective Pictet–Spengler cyclization, cleavage of the carbamate and removal of the ester protecting group on the phenol by hydrazinolysis readily gave the cherylline-type precursor **5** in 91% overall yield. For the selective Pictet–Spengler transformation, the presence of an alkoxycarbonyl group ($R = CO_2Et$) in **4** was essential for the observed site selectivity,[15] as it decreased the nucleophilicity of ring E by its electron-withdrawing effect.

With the chiral cherylline-type building block **5** in hand, we chemically explored the feasibility of the proposed bioinspired approach to the montanine-type pentacyclic skeleton (Scheme 6). On the basis of recent progress in



Scheme 5. Asymmetric synthesis of the cherylline-type precursor.



Scheme 6. Bioinspired tandem oxidative dearomatization/intramolecular aza-Michael addition.

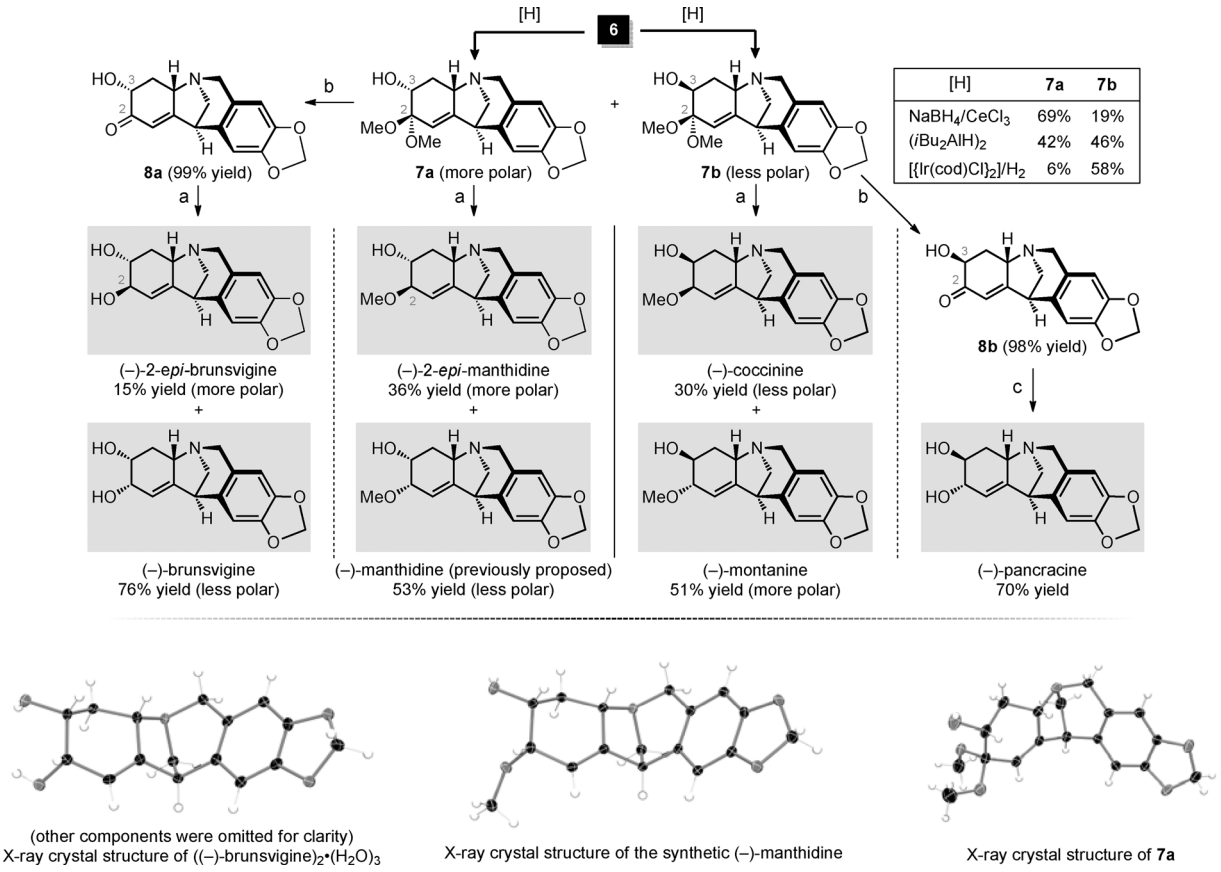
hypervalent-iodine-mediated phenol dearomatization,[16] we subjected the substituted isoquinoline **5** bearing a free secondary-amine moiety to the preliminarily optimized conditions with $PhI(OAc)_2$ as an oxidant and MeOH as the solvent in the presence of CF_3CO_2H.[17] Significantly, our proposed key tandem oxidative dearomatization/intramolecular aza-Michael addition proceeded smoothly with high diastereoselectivity via an *ortho*-quinone monoketal intermediate.[18,19] This tandem reaction led exclusively to the multifunctionalized chiral intermediate **6** (99% *ee*) with the 5,11-methanomorphanthridine core in 61% yield. The absolute configuration of **6** was established unambiguously by X-ray crystallographic analysis.[20,21]

To account for the observed stereoselectivity of this bioinspired transformation, we propose a plausible model based on the Curtin–Hammett principle (Scheme 6).[22] On the basis of kinetic accessibility in the intramolecular aza-1,4-conjugate addition of the *ortho*-quinone monoketal intermediate formed in situ, two main conformers **G2** and **G3** would be adopted in the current addition reaction. Owing to the presence of energetically unfavorable 1,3-allylic strain in **G2**,[23] the excellent diastereoselectivity of this tandem reaction might be appropriately rationalized by a preferential *Si*-face attack of the enone moiety via the kinetically accessible conformer **G3**.

Having established the crucial 5,11-methanomorphanthridine pentacyclic framework with the requisite configuration and functionality in **6**, we then pursued the divergent asymmetric synthesis of montanine-type alkaloids (Scheme 7). To access the stereochemically defined C3–OH group in ring E of the target alkaloids (Scheme 4), we examined the diastereoselective reduction of the diketone monoketal **6**.[24] The resulting diastereomers **7a** (equatorial C3–OH) and **7b** (axial C3–OH)[9c] could be separated chromatographically. Interestingly, the Luche reduction of ketone **6** ($NaBH_4/CeCl_3$) gave **7a** as the main product in 69% yield, whereas the iridium-catalyzed hydrogenation of **6** ($[\{Ir(cod)Cl\}_2]/H_2$)[25] gave **7b** as the main product in 58% yield.[24] The absolute configuration of **7a** was unequivocally assigned by X-ray crystallographic analysis.[20,21]

After the above reduction of the C3 carbonyl group in **6**, the further reduction of the C2 ketal moiety of less polar **7b** with $(i\text{Bu}_2\text{AlH})_2$[9c] directly furnished readily separable (−)-montanine[3a,c,9c] and (−)-coccinine[3a,c,9b,c] in 51 and 30% yield, respectively (Scheme 7). Analogously, when more polar **7a** was subjected to reduction with $(i\text{Bu}_2\text{AlH})_2$, (−)-manthidine originally assigned by Wildman[3a,c] was obtained readily for the first time in 53% yield, together with separable (−)-2-*epi*-manthidine in 36% yield. The configuration of our synthetic sample as that previously proposed for (−)-manthidine[3c,26] was definitively confirmed by X-ray crystallographic analysis.[20,21]

To further demonstrate the synthetic diversity of our current strategy (Scheme 7), we subjected **7a** and **7b** to acidic ketal hydrolysis in parallel and obtained ketone **8a** (equatorial C3–OH)[27] and **8b** (axial C3–OH)[6a,27] in 99 and 98% yield, respectively. Upon the treatment of **8a** with $(i\text{Bu}_2\text{AlH})_2$ at −78 °C, readily separable (−)-brunsvigine and (−)-2-*epi*-brunsvigine were obtained in 76 and 15% yield, respectively.



(other components were omitted for clarity)
X-ray crystal structure of $((-)\text{-brunsvigine})_2 \cdot (H_2O)_3$

X-ray crystal structure of the synthetic (–)-manthidine

X-ray crystal structure of **7a**

Scheme 7. Divergent asymmetric synthesis of (−)-montanine, (−)-coccinine, (−)-brunsvigine, (−)-pancracine, and previously proposed (−)-manthidine: a) $(i\text{Bu}_2\text{AlH})_2$, CH_2Cl_2; b) oxalic acid, THF/H_2O; c) $NaBH(OAc)_3$, $CH_3CN/AcOH$. cod = 1,5-cyclooctadiene.

The configuration of (−)-brunsvigine[3b,e,f,6f,j] was also elucidated by X-ray crystallographic analysis.[20,21] Meanwhile, the mild reduction of **8b** by $NaBH(OAc)_3$ exclusively gave (−)-pancracine[3d,6a] in 70% yield.

In conclusion, a new strategy featuring a bioinspired tandem oxidative dearomatization/intramolecular aza-Michael addition was developed for a diversity-oriented, expeditious asymmetric total synthesis of five montanine-type *Amaryllidaceae* alkaloids. Significantly, an unusual conversion of the cherylline-type isoquinoline skeleton into the unique 5,11-methanomorphanthridine core of montanine-type alkaloids was proposed and chemically explored. In comparison with previous synthetic studies, it is particularly noteworthy that our bioinspired strategy positively enables a step-economic, effective, divergent, and enantioselective route to (−)-montanine (8 steps, 11% yield), (−)-coccinine (8 steps, 6.5% yield), (−)-brunsvigine (9 steps, 19% yield), and (−)-pancracine (9 steps, 15% yield), as well as previously proposed (−)-manthidine (8 steps, 14% yield). The current investigation not only synthetically provides a bridge between the cherylline-type and montanine-type alkaloids, but also manifests the potential of bioinspired design in the chemical synthesis of natural products.

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Keywords: alkaloids · bioinspired synthesis · dearomatization · domino reactions · total synthesis

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[15] For this electrophilic aromatic substitution, the electronic difference between ring B and ring E in **4** is mainly responsible for the observed site selectivity. In general, the nucleophilicity of a methylenedioxy-substituted phenyl ring is lower than that of an analogous dimethoxy-substituted phenyl ring (electron-donating group) owing to the stereoelectronic effect of the rigid methylenedioxy substituent (poor overlap between the oxygen lone pair of electrons and the phenyl π system). For related reports, see: a) C.-K. Sha, J.-J. Young, C.-P. Yeh, S.-C. Chang, S.-L. Wang, *J. Org. Chem.* **1991**, *56*, 2694; b) W.-D. Z. Li, X.-W. Wang, *Org. Lett.* **2007**, *9*, 1211. In principle, therefore, the desired site-selective installation of a methylene unit in ring B (the methylenedioxy-substituted phenyl ring) of **4** could be expected upon the introduction of an electron-withdrawing group (e.g., $R = CO_2Et$) to ring E of **4**. For one example of a site-selective Pictet–Spengler cyclization between two electronically different aromatic rings, see: c) X. L. Wang, X. F. Zheng, R. H. Liu, J. Reiner, J. B. Chang, *Tetrahedron* **2007**, *63*, 3389.

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brunsvigine)$_2$·(H_2O)$_3$}, and 955424 (synthetic (−)-manthidine) contain 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.

[21] For an ORTEP drawing from a different perspective, see the Supporting Information.

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[27] A diastereoselective kinetic resolution of a mixture of **8a** and **8b** under silylation conditions (iPr$_3$SiOSO$_2$CF$_3$, iPr$_2$NEt, −78 °C) was discovered: the silylation of α-hydroxyketone **8a** with an equatorial C3−OH group was kinetically much faster than that of **8b** with an axial C3−OH group. This process provides an alternative to the individual preparation of **8a** and **8b**. See the Supporting Information for details.