Alkaloids

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Enantioselective Synthesis and Racemization of (−)-Sinoracutine

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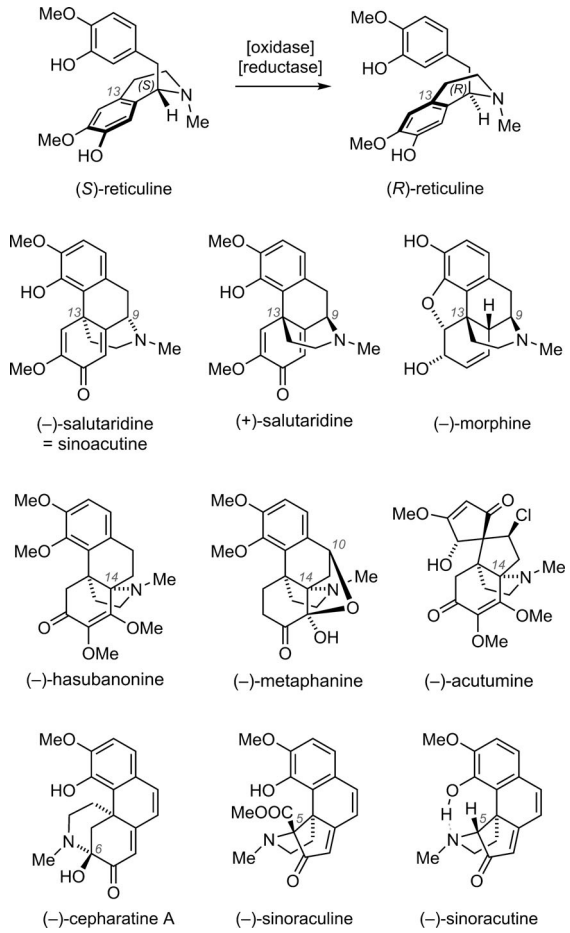
Dedicated to Professor Gilbert Stork

Abstract: *Sinoracutine is a recently isolated alkaloid with unusual stereochemical and biological properties. It features an unprecedented tetracyclic 6/6/5/5 skeleton that bears an N-methylpyrrolidine ring fused to a cyclopentenone. Interestingly, both enantiomers of sinoracutine have been independently isolated from the same plant, yet the molecule does not appear to occur as a racemate. Here, we present a short synthesis of (−)-sinoracutine that relies on a highly diastereoselective Pauson–Khand reaction and a Mandai–Claisen reaction to install the quaternary stereocenter. Our work establishes the absolute configuration of the levorotatory isomer and suggests that the optical purity of sinoracutine varies in nature due to its gradual racemization. Experimental evidence supports this proposal, and a plausible mechanism for the racemization is provided.*

(*S*)-Reticuline and its enantiomer (*R*)-reticuline are key intermediates in the biosynthesis of a variety of important alkaloids (Scheme 1). The former can be isomerized to the latter through a series of enzymatic steps[1,2] and both can undergo phenolic couplings and further downstream transformations to generate a vast array of molecules. Most of these possess a quaternary stereocenter in benzylic position, to which a two-carbon chain terminating in a nitrogen is attached. This nitrogen can be connected to the remainder of the skeleton at different positions to provide structures that contain various five- or six-membered heterocycles.

In the (*R*)-series, phenolic coupling of initially leads to (+)-salutaridine, from which the morphine alkaloids are derived. The analogous reaction in the (*S*)-series affords (−)-salutaridine, which was initially named sinoacutine. It was first isolated from *Sinomenium acutum*, a member of the Menispermaceae family. A migration of the C–N bond from C9 to C14 in sinoacutine or a related intermediate contracts the piperidine ring and affords the hasubanan alkaloids, which feature a pyrrolidine ring. They are exemplified here by hasubanonine. Further oxidations at C10 and additional ring contractions can occur, which yield alkaloids such as metaphanine and acutumine, respectively.[3–7]



Scheme 1. Structural diversity of alkaloids derived from reticuline.

The occurrence of enantiomeric natural products in different producing organisms is well documented but the isolation of a racemate or a scalemic mixture from the same producing organism is rare.[8,9] Therefore, we were intrigued by several recent reports on a new alkaloid termed sinoracutine. The first one, published in 2009, described the isolation of a levorotatory isomer from *Sinomenium acutum*.[10] Its optical rotation was measured as $[\alpha]_D^{25} = -7.4$ ($c = 0.35$, $CHCl_3$) and an X-ray structure was reported that features a racemate and not a single enantiomer. One year later, the "optical isomer" (+)-sinoracutine was isolated from the same plant.[11] Unfortunately, no optical rotation was reported in this case. The assigned structure was confirmed by a second X-ray analysis that again featured the racemate. In 2010, (−)-sinoracutine was also found to occur in *Stephania cepharantha*, another member of the Menispermaceae family.

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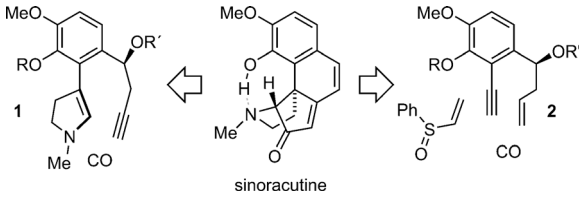
In this case, the optical rotation was reported to be considerably higher, $[\alpha]_D^{25} = -754.5$ ($c = 1.14$, $CHCl_3$).[12]

Sinoracutine has some unusual and attractive structural features. Compared to other reticuline-derived alkaloids, it lacks one carbon atom, which is presumably lost through decarboxylation. This hypothesis is supported by the recent isolation of sinoraculine, the carboxymethyl analogue of sinoracutine, from *Stephania cepharanta*.[13] Furthermore, sinoracutine possesses a cyclopentenone and an *N*-methylpyrrolidine ring that is connected to the remaining carbon skeleton at C5. This motif had not been observed previously in hasubanan and morphine alkaloids. It also features an extended π-system that presumably arises from several oxidations and eliminations.[14] An intramolecular hydrogen bond between the phenolic hydroxyl and the tertiary amine renders sinoracutine more lipophilic than structurally related compounds with a free phenol and a tertiary amine. In terms of its bioactivity, (−)-sinoracutine was shown to increase cell viability against hydrogen peroxide induced damage in PC12 cells. As such, it could serve as a template for new neuroprotective agents.[10]

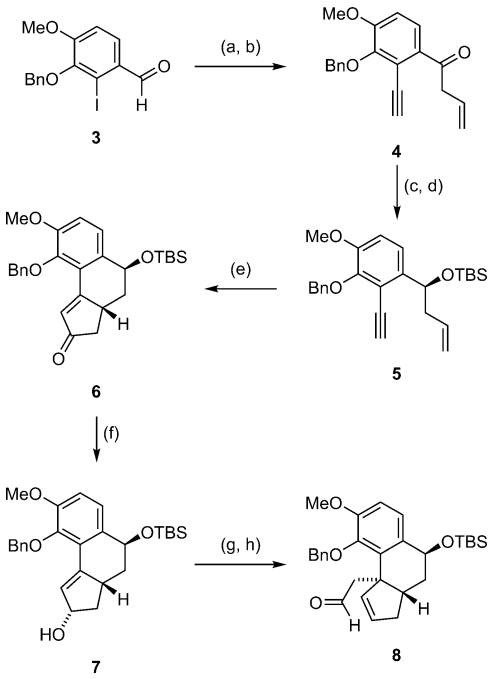
The unanswered questions concerning the optical purity of sinoracutine, its attractive structure, and its bioactivity prompted us to devise a synthetic route that could access the natural product in racemic as well as in enantiopure form. Our retrosynthetic analysis is shown in Scheme 2. It was based



Scheme 2. Retrosynthesis via Pauson–Khand reactions.

on our desire to install the five-membered ring through a Pauson–Khand reaction. Initial attempts were geared toward enamine-ynes of type **1**.[15–18] This plan was ultimately discarded due to our failure to develop a satisfying asymmetric synthesis of such a precursor. We therefore turned our attention to enynes of type **2**. Although the benzylic quaternary stereocenter could not be directly installed using such an approach, it provided a short route to the target molecule that could be easily rendered asymmetric.

The synthesis began with the known isovanillin derivative **3**, which had been previously employed in Overman's elegant total synthesis of morphine (Scheme 3).[19] Sonogashira coupling with trimethylsilylacetylene followed by addition of allylmagnesium bromide and in situ desilylation furnished an allylic alcohol which was oxidized to **4** with Dess–Martin periodinane. Enantioselective reduction was best accomplished (96% *ee*) with (−)-*B*-chlorodiisopinocampheylborane and delivered silyl ether **5** after treatment with *tert*-butyldimethylchlorosilane (TBSCl).[20–22] Several direct asymmetric allylation protocols investigated failed, underscoring the recalcitrance of *o*-substituted benzaldehydes to undergo stereoselective catalytic allylation reactions.[23–25] In the racemic series **5** could be made directly from **2** via allylation and protection (see the Supporting Information).

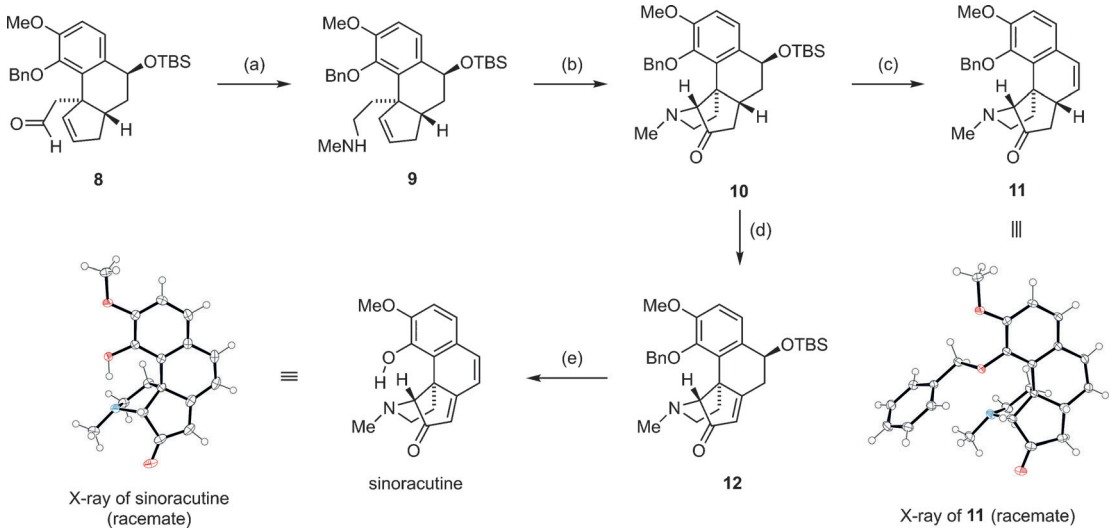


Scheme 3. Stereoselective synthesis of tricycle **8**. a) TMSCCH, Et_3N, CuI, $Pd(PPh_3)_2Cl_2$, THF, 60 °C, then allylMgBr 0 °C, then KOH, MeOH, 0 °C to RT, 74% overall; b) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to RT, 66%; c) (−)-*B*-chlorodiisopinocampheylborane, −60 °C to −40 °C, 72%; d) *tert*-butyldimethylchlorosilane, imidazole, DMF, RT, 89%; e) $Co_2(CO)_8$, 1,2-dichloroethane, then trimethylamine *N*-oxide dihydrate, 0 °C to RT, 70%; f) $LiAlH_4$, Et_2O, 0 °C, 98%; g) NaH, THF; then phenyl vinyl sulfoxide, KH, 0 °C to RT; h) $NaHCO_3$, 1,2-dichlorobenzene, 176 °C; 57% over 2 steps.

The Pauson–Khand reaction of **5** under oxidative conditions delivered tricycle **6** in good yield and as a single diastereoisomer whose absolute configuration was assigned by X-ray analysis.[42] The stereochemical control of this reaction is attributable to the bulky benzylic TBS ether of **5** which conformationally locks the aryl-alkyne.[26,27] This substrate outperformed its free hydroxy and acetoxy analogues in terms of yield and diastereoselectivity. The subsequent 1,2-reduction proceeded stereoselectively from the top face to deliver allylic alcohol **7** in excellent yield.

Attempts to introduce the benzylic quaternary stereocenter by Eschenmoser and Johnson–Claisen reactions were not successful; neither was the thermal rearrangement of a preformed vinyl ether.[28–31] Ultimately, we resorted to a two-step protocol developed by Mandai: Michael-type addition of **7** to phenyl vinyl sulfoxide gave an intermediate sulfoxide that underwent elimination of sulfenic acid and subsequent sigmatropic rearrangement at high temperature to afford aldehyde **8**.[32,33] This stereoselective sequence installed the crucial benzylic quaternary stereocenter and set the stage for the formation of the next ring.

With aldehyde **8** in hand we proceeded to introduce the nitrogen and complete the synthesis (Scheme 4). Reductive amination of **8** proceeded as planned and gave secondary amine **9.** The *cis*-fused pyrrolidinocyclopentenone was intro-



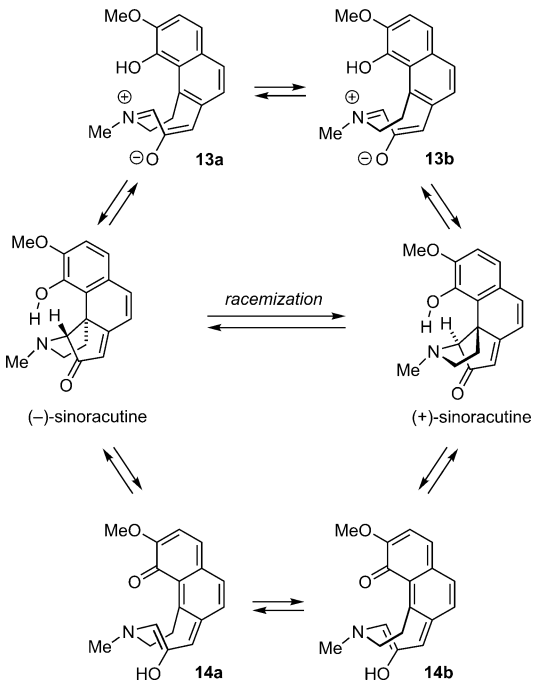
Scheme 4. Completion of the synthesis. a) $MeNH_2$, $MgSO_4$, then $NaBH_4$, MeOH, 0 °C to RT, 97%; b) *N*-iodosuccinimide, CH_2Cl_2, then evaporation; dimethylsulfoxide, Et_3N, RT, 64%; c) camphor-10-sulfonic acid, benzene, RT, 69%; d) lithium diisopropylamide, THF, −78 °C, then *N*-*tert*-butylbenzenesulfinimidoyl chloride, −78 °C, 87%; e) trifluoroacetic acid, pentamethylbenzene, 0 °C to 40 °C, 73%.

duced using a tandem iodoamination–Kornblum oxidation. To this end, **9** was dissolved in CH_2Cl_2 and treated with 2 equiv of *N*-iodosuccinimide to afford an intermediate iodoamine that proved unstable to aqueous workup. However, evaporation of the solvent, followed by dissolution of the intermediate in dimethyl sulfoxide and addition of triethylamine, delivered the α-amino ketone **10** in good yield. The addition of silver salts, which are routinely employed to facilitate analogous oxidations, was not necessary, probably due to neighboring group participation of the tertiary amine.[34,35] Elimination of TBS-OH under acidic conditions then gave tetracycle **11**, whose relative configuration was confirmed by an X-ray analysis of the racemic compound.

(−)-Sinoracutine could be reached from **11** but we found it more convenient to access it from intermediate **10**. Mukaiyama oxidation[36] of Kornblum product **10** gave cyclopentenone **12**, which was treated with trifluoroacetic acid.[37,38] This resulted both in elimination of the silyl alcohol and in debenzylation and afforded sinoracutine in one step. In the racemic series, we obtained crystals of (±)-sinoracutine that were suitable for X-ray analysis.

The spectral data of our synthetic material were in full agreement with those of the natural isolate and HPLC analysis on a chiral stationary phase confirmed the enantiomeric purity of our synthetic material. The optical rotation was determined to be $[\alpha]_D^{25} = -1067.3$ ($c = 0.35$, $CHCl_3$). This unusually high value may be due to the rigidity and twist of the extended π-system. Comparison of the crystallographic data of purported (+)-sinoracutine[11] and that of our racemic material revealed that both crystals have identical cell parameters and belong to the centrosymmetric space group *Pbca* whose unit cell contains both enantiomers. Furthermore, the reported X-ray structure of purported (−)-sinoracutine also exhibited a centrosymmetric unit cell with both enantiomers present, namely $P2_1/n$. It was erroneously reported as the chiral space group $P2_1$.[10] Taken together, these data suggest that in *Sinomenium acutum*, sinoracutine occurs in scalemic form and that the racemate crystallizes preferentially.[39] The large difference in absolute value of the optical rotations indicates that (−)-sinoracutine isolated from *Stephania cepharanta* is also scalemic albeit of higher optical purity than the material derived from *Sinomenium acutum*.

From a biosynthetic point of view, it seems unlikely that the oxidative phenolic coupling and subsequent downstream processing occurs for both enantiomers of reticuline. This left us with the possibility that (−)-sinoracutine undergoes racemization once it is formed. Two reasonable mechanisms for this racemization are shown in Scheme 5. They could



Scheme 5. Proposed mechanism for the racemization of sinoracutine.

involve either a retro-Mannich/Mannich sequence through **13a/b**, or, proceed by proton transfer, ring opening, and closure via quinone methides **14a/b**. Racemization of complex alkaloids through intricate mechanisms have indeed been observed before, for instance in indole alkaloids.[40]

The racemization could be verified experimentally. When a sample of the alkaloid with 98.9% *ee* in a solution of *n*-heptane/*i*-PrOH/MeOH = 6/2/2 was kept at room temperature for 67 days, we noticed a very small but measurable erosion of enantiopurity to 95.7% *ee*. This process could be accelerated thermally: heating the sample to 60 °C for 5 days delivered a nearly racemic product (3.2% *ee*). Notably, no racemization had occurred during the last step of our synthesis (debenzylation/elimination), where sinoracutine was kept in warm trifluoroacetic acid for hours. Under these conditions it can be assumed, however, that the nitrogen is fully protonated.

In conclusion, we have achieved a short and stereoselective synthesis of the recently isolated alkaloid sinoracutine.[41] It hinges on the efficient translation of stereochemical information from a readily prepared enantiopure allylic alcohol and used a Claisen rearrangement and a iodoamination/oxidation sequence to install the two stereocenters of the target molecule. Our synthesis could also provide a convenient entry to C10-oxygenated hasubanan-type alkaloids following a ring expansion of the cyclopentanone ring. Synthetic (−)- and (±)-sinoracutine will be subjected to further biological testing to assess the activity of the racemic as well as the enantiomerically pure natural product. Furthermore, theoretical studies to elucidate the exact mechanism of racemization are underway and will be reported in due course.

Acknowledgements

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Keywords: alkaloids · asymmetric synthesis · Kornblum oxidation · Pauson–Khand reaction · sigmatropic rearrangement

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[39] Indeed, we have not yet been able to obtain X-ray quality crystals of enantiomerically pure (−)-sinoracutine.
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[41] While our work was in revision, a semisynthesis of sinoracutine from sinomenine was published, where the installation of the quaternary benzylic carbon proceeds via an unusual skeletal rearrangement. The spectral data of this product match our spectral data for sinoracutine, but were apparently not recognized as such. A. Garcia, B. S. Drown, P. J. Hergenrother, *Org. Lett.* **2016**, *18*, 4852 – 4855.
[42] CCDC 1499488 (**6**), 1499484 (**11**), and 1499488 ((±)-sinoracutine) contain the complete crystallographic data for this paper. These data can be obtained free of charge upon request from The Cambridge Crystallographic Data Centre.

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Communications

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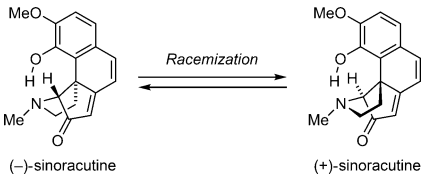
Enantioselective Synthesis and Racemization of (−)-Sinoracutine



Make and mix: A synthesis of the unusual alkaloid (−)-sinoracutine relies on a diastereoselective Pauson–Khand reaction and a Mandai–Claisen rearrangement to install the quaternary stereocenter. Studies establish the absolute configuration of the levorotatory isomer and suggest that optical purity of the natural product is determined by slow racemization.