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Synthesis of (±)-3*H*-Epivincamine via a Rh(II)-Triggered Cyclization/Cycloaddition Cascade

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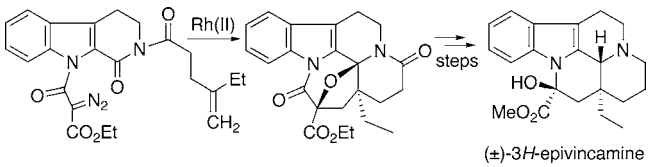
ABSTRACT



A synthesis of (±)-3*H*-epivincamine is reported. Important steps include (1) a Rh(II)-catalyzed intramolecular [3+2]-cycloaddition of an α-diazo indolo amide, (2) a reductive ring opening of the cycloadduct, (3) a decarboethoxylation reaction, and (4) a base-induced keto-amide ring contraction.

Vinca alkaloids comprise a large group of biologically active, naturally occurring bases, isolated from several plants of the *Vinca* genus.[1] Members of this family of alkaloids have been used for the treatment of cognitive and behavioral symptoms associated with vascular and degenerative disorders of the central nervous system.[2] (+)-Vincamine (**1**) and (−)-eburnamonine (**2**) as well as (±)-3*H*-epivincamine (**3**) all exhibit strong vasodilation activity which brings about an enhancement of the overall cerebral blood flow.[3,4] Thus, these compounds along with their semisynthetic derivatives have recently been the subject of intense pharmacological and synthetic studies.[5] These natural products all share a common pentacyclic framework which generally contain a cis-fused D/E ring system (Figure 1), although there are some examples of related alkaloids possessing the trans-fused junction.[6] Several strategies for the synthesis of vincamine (**1**) and its structural analogues have been reported.[7] The most common feature of these approaches is to first establish the [ABCD]-type octahydroindolo[2,3-*a*]quinolizine system (i.e., **4**) starting from an indole subunit and then complete the

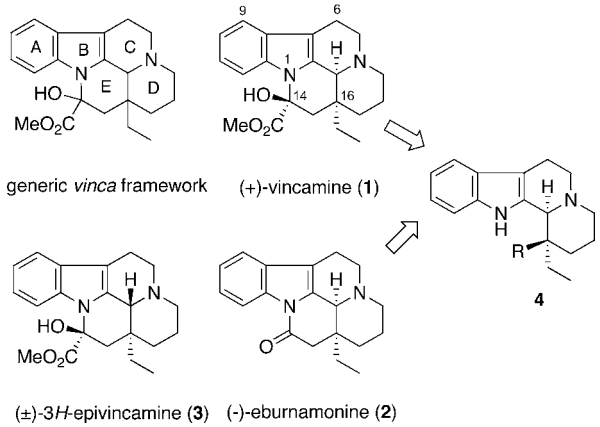


Figure 1. Common pentacyclic framework of vinca alkaloid family.

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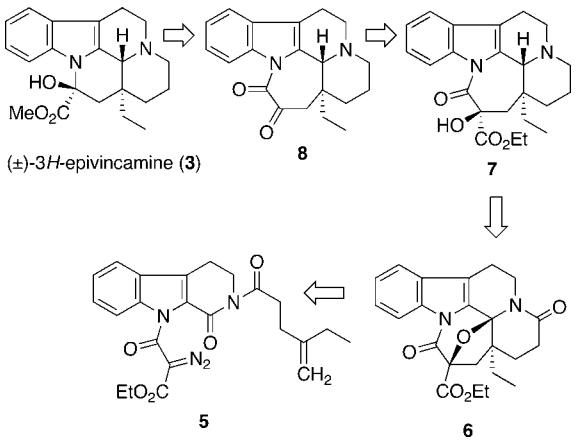
synthesis of the specific target by appending the final E-ring.[2] Methods for building up the requisite gem-disubstituted tetracyclic [ABCD]-framework **4** usually involve a Pictet−Spengler/Bischler−Napieralski cyclization,[8] a Michael-type alkylation of the so-called "Wenkert enamine",[9] or an annulation reaction of a dihydro-β-carboline derivative.[10]

Our approach to the *Vinca* alkaloids was guided by a long standing interest in the intramolecular [3+2]-cycloaddition of carbonyl ylide dipoles.[11] The generation of onium ylides by a transition-metal-promoted cyclization reaction has emerged in recent years as an important and efficient method for the assembly of ring systems that are difficult to prepare by other means.[12,13] In earlier work from our laboratory, we had described the formation of push−pull dipoles from the Rh(II)-catalyzed reaction of α-diazo amides and noted that a smooth intramolecular 1,3-dipolar cycloaddition occurred across alkenyl π-bonds to provide novel pentacyclic compounds in good yield and in a stereocontrolled fashion.[14] Herein we report a concise synthesis of (±)-3*H*-epivincamine (**3**), first isolated by Cava in 1968[6] according to the plan outlined in Scheme 1. The key intermediate **6** is readily assembled by a Rh(II)-catalyzed cyclization/dipolar cycloaddition sequence starting from α-diazo indolo amide **5**. Reductive ring opening of the resulting cycloadduct **6** is then marshalled to create the trans-pentacyclic skeleton found in (±)-3*H*-epivincamine (**3**). Finally, a base-induced ring contraction is exploited to complete the synthesis of **3**. The

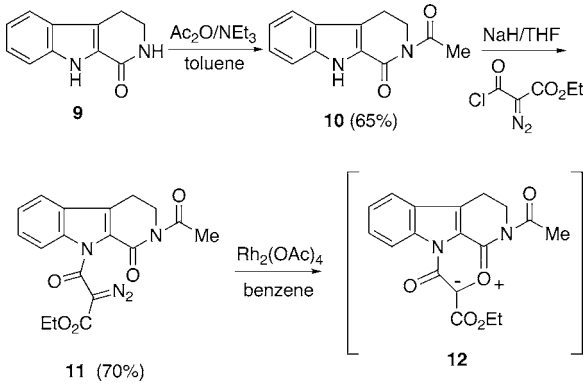
Scheme 1



successful completion of this synthesis demonstrates the utility of our cascade methodology for the construction of complex indole-containing natural products.

For the initial investigations into the tandem process, we chose to examine the reactivity under Rh(II) catalysis conditions of α-diazo amide **11**, a test substrate. Compound **11** was readily prepared by treating carboline **9** with acetic anhydride under refluxing conditions followed by reaction of the resulting *N*-acetyl carboline **10** with sodium hydride and ethyl 2-diazomalonyl chloride[15] (Scheme 2). Heating

Scheme 2



compound **11** with catalytic $Rh_2(OAc)_4$ generates a rhodium carbenoid intermediate which undergoes cyclization with the neighboring amido carbonyl group to form a transient carbonyl ylide dipole **12**. Subsequent bimolecular trapping of the dipole with various common dipolarophiles led to the expected [3+2]-cycloadducts.[12] Table 1 illustrates the scope of the cycloaddition by showcasing the reaction with a variety of commercially available dipolarophiles. In a typical experiment, heating a sample of **11** with catalytic amounts of $Rh_2(OAc)_4$ in benzene at 80 °C in the presence of an equivalent

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(10) (a) Oppolzer, W.; Hauth, H.; Pfäffli, P.; Wenger, R. *Helv. Chim. Acta* **1977**, *60*, 1801. (b) Hugel, G.; Lévy, J.; Le Men, J. *C. R. Acad. Sci.* **1972**, *274*, 1350. (c) Danieli, B.; Lesma, G.; Palmisano, G. *J. Chem. Soc., Chem Commun.* **1981**, 908. (d) Magnus, P.; Pappalardo, P.; Southwell, I. *Tetrahedron* **1986**, *42*, 3215.

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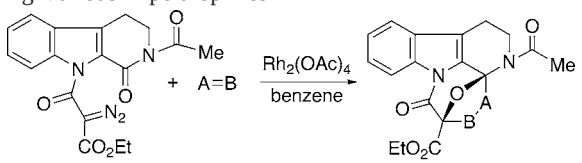
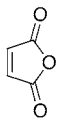
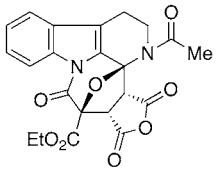
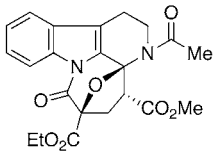
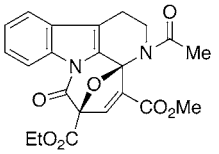
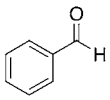
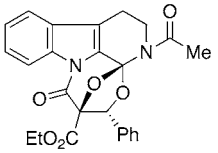
Table 1. Bimolecular Cycloadditions of Diazo Amide **11** Using Various Dipolarophiles



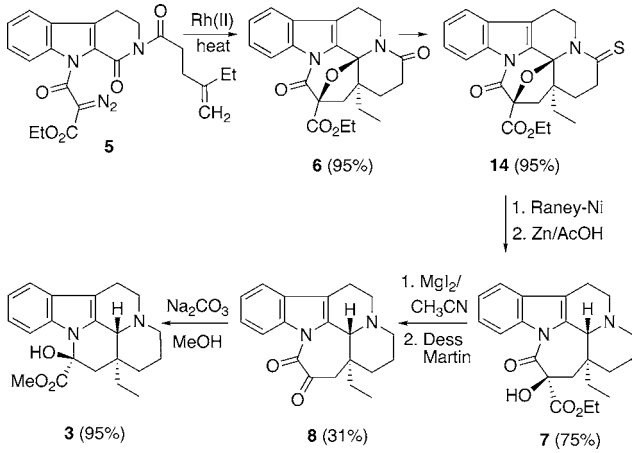
11 **13**

entry	dipolarophile	product (yield)
1		 **13a** (75%)
2		 **13b** (77%)
3		 **13c** (78%)
4		 **13d** (85%)

of a trapping agent affords cycloadducts **13a**−**13d** in 75−85% yield and with complete diastereoselectivity. In general, the cascade reaction sequence produced only the endo-cycloaddition product isolated as a single diastereomer.

An optimized sequence for the diastereoselective synthesis of (±)-3*H*-epivincamine (**3**) following the above-mentioned strategy is shown in Scheme 3. The readily available carboline **9** was treated with the mixed anhydride of 4-methylenehexanoic acid to give 2-(4-methylenehexanoyl)-2,3,4,9-tetrahydro-1*H*-pyrido-[3,4-*b*]indol-1-one. Deprotonation of the indole N−H with sodium hydride followed by reaction with ethyl 2-diazo malonyl chloride gave α-diazo indolo amide **5** in 60% yield. The critical intramolecular dipolar-cycloaddition was achieved by heating a solution of **5** with $Rh_2(OAc)_4$ (1 mol %) in refluxing benzene. Under these conditions, the key intermediate **6** was obtained in 95% yield and with complete diastereoselectivity as evidenced by

Scheme 3



5 **6** (95%) **14** (95%)

3 (95%) **8** (31%) **7** (75%)

its ^{1}H NMR spectrum. The relative sterochemical configurations within **6** are a consequence of endo cycloaddition with regard to the dipole, and this is in full accord with the lowest-energy transition state.[16]

The uniquely functionalized oxapolycyclic adduct **6** contains a "masked" *N*-acyliminium ion which can be released by treatment with a Lewis acid.[17] However, our initial attempts to reduce the resulting iminium ion with Et_3SiH and other hydride reagents afforded only recovered starting material. We suspected that removal of the lactam carbonyl group would help promote the reduction by enhancing the nucleophilicity of the nitrogen atom thereby facilitating oxabicyclic ring opening. Accordingly, cycloadduct **6** was converted into the corresponding thiolactam **14** with Lawesson's reagent in 95% yield. Reductive removal of the thiocarbonyl group with Raney−Ni followed by treatment of the resulting piperidine with Zn/AcOH gave the ring-opened amide **7** containing the trans D/E ring fusion of *3H*-epivincamine in 75% yield over the two steps. Reduction of the transient iminium ion with zinc occurred from the least hindered face and generated the required trans ring junction.[18] Next, the carboethoxy group was selectively removed following experimental conditions previously developed in our laboratory.[19] Thus, treatment of **7** with MgI_2 in refluxing acetonitrile containing trace amounts of water resulted in the formation of an α-hydroxy lactam in 62% yield. The reaction was shown to proceed via a novel α-hydroxy-*β*-dicarbonyl to α-ketol ester rearrangement via a transient carbonate intermediate.[19,20] Oxidation of the secondary alcohol to the corresponding keto amide **8** was performed using Dess−Martin periodinane in 50% yield. The conversion of related

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(17) Padwa, A.; Zhang, H. *J. Org. Chem.* **2007**, *72*, 2570.

(18) All of our efforts using a variety of reducing agents only resulted in the formation of the trans-ring sterochemistry. Studies are currently underway toward an enantioselective synthesis of **3** using a chiral catalyst in the iminium ion reduction step.

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oxolactams to vincamine derivatives has been reported in the literature.[10a,21] In our hands, methanolysis of **8** with sodium carbonate as base gave, after 1 h of stirring at room temperature, a 95% yield of (±)-3*H*-epivincamine (**3**) as the only diastereomer.

In summary, a concise synthesis of the *Vinca* alkaloid (±)-3*H*-epivincamine (**3**) is reported. A central step in the synthesis consists of an intramolecular [3+2]-cycloaddition reaction of an α-diazo indolo amide which delivers the pentacyclic skeleton of the natural product in excellent yield. The acid lability of the oxabicyclic structure was exploited to establish the trans D/E ring fusion. Finally, a base induced keto-amide ring contraction was utilized to generate the E-ring of the natural product. The short sequence of reactions used to synthesize (±)-3*H*-epivincamine (**3**) should also provide a rapid entry into other *Vinca* alkaloids and is currently under active investigation in our laboratories.

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Supporting Information Available: Complete description of experimental details and product characterization of all new compounds together with photocopies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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