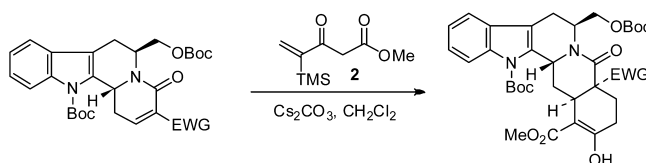


Preparation and Double Michael Addition
Reactions of a Synthetic Equivalent of the
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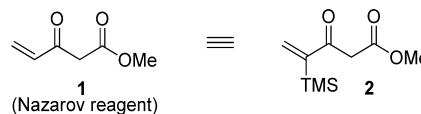
ABSTRACT



A synthetic equivalent of the Nazarov reagent, the silyl derivative **2**, able to undergo base-catalyzed double Michael addition reactions with α,β -unsaturated carbonyl compounds has been developed. The new reagent satisfactorily reacts with unsaturated indolo[2,3-*a*]quinolizidine lactams to give pentacyclic yohimbine-type derivatives.

The Nazarov reagent (methyl or ethyl 3-oxo-4-pentenoate)¹ is a well-known annelating agent that has been extensively used in terpene and alkaloid syntheses.² Its usefulness and synthetic versatility stem from its dense functionalization, with a nucleophilic acidic carbon in the β -keto ester moiety and an electrophilic carbon included in an α,β -unsaturated ketone fragment (Scheme 1). The Nazarov reagent (**1**) has successfully been used in a variety of Robinson-type annulations with enolizable

Scheme 1. A Synthetic Equivalent of the Nazarov Reagent



ketones,³ β -dicarbonyl compounds,⁴ enamino esters,⁵ imines,⁶ enamines,⁷ dienamines,⁸ and (thio)imides,⁹ in which the reagent undergoes an initial Michael addition and the resulting β -keto ester enolate acts as a nucleophile.

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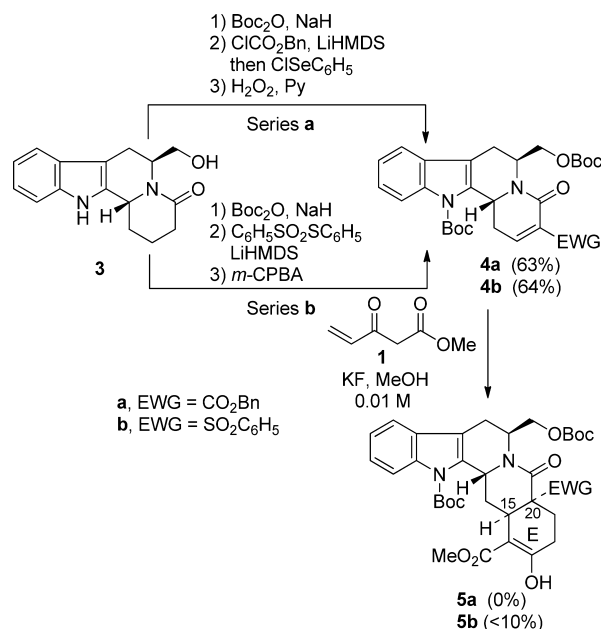
However, the instability of **1** under basic conditions¹⁰ has restricted its use in annulations with α,β -unsaturated carbonyl derivatives, in which the reagent successively acts as a Michael donor and a Michael acceptor.^{11,12} To overcome this limitation, as well as the difficulties associated with the preparation and purification of the Nazarov reagent, more stable modified reagents substituted at the olefinic carbons¹³ and suitable precursors allowing its *in situ* generation¹⁴ have been developed. In contrast with the original Nazarov reagent, the substituted reagents, extensively used by Deslongchamps, react in their enolate form, smoothly undergoing base-catalyzed double Michael addition reactions to give *cis*-decalin derivatives.¹³

In this letter we present a stable and practical synthetic equivalent of the Nazarov reagent, the silyl derivative **2**, that we have developed in the context of our studies on the use of tryptophanol-derived lactams in the enantioselective synthesis of indole alkaloids.¹⁵ We envisaged a straightforward approach to pentacyclic yohimbine-type derivatives, in which the carbocyclic E ring would be assembled by a double Michael addition of the Nazarov reagent (**1**) to unsaturated indoloquinolizidine lactams **4**. These lactams, which incorporate an additional activating electron-withdrawing substituent, were prepared in good overall yields by conventional methods from the known lactam **3**,¹⁶ as outlined in Scheme 2.

Initial attempts to perform the annulation of the Nazarov reagent **1** with unsaturated lactam **4a** ($\text{Cs}_2\text{CO}_3/\text{CH}_2\text{Cl}_2$ or KF/MeOH) were unsuccessful, resulting in complete degradation of **1**. When using lactam **4b**, which bears a benzenesulfonyl activating substituent, annulation occurred to some extent, pentacycle **5b** being isolated in very low yield from the resulting complex mixture.

Despite these unsatisfactory results, the viability of our double Michael addition strategy was confirmed by the successful Cs_2CO_3 -mediated reaction of the more stable

Scheme 2. Attempted Double Michael Addition with the Nazarov Reagent, **1**



methyl substituted Nazarov reagent **6**¹⁷ with the above lactams **4a** and **4b** to give the respective pentacyclic derivatives **8a** and **8b** as single stereoisomers in excellent yields¹⁸ (Scheme 3). Although it was possible to stereoselectively remove the benzenesulfonyl group of **8b** with retention of the configuration,¹⁹ the presence of the methyl substituent in the carbocyclic E ring makes pentacyclic derivative **9** unsuitable for the synthesis of yohimbine-type natural products.

At this point, we decided to design a synthetic equivalent of the Nazarov reagent that would overcome the inconveniences and limitations of the original reagent **1**. Bearing in mind that α -silylated vinyl ketones have been extensively used as surrogate vinyl ketones in annulation reactions,²⁰ we planned to prepare a Nazarov-type reagent, such as **2**, silylated at the α -position of the enone (Scheme 4). The α -trimethylsilyl group would increase the electrophilicity of the β -carbon, stabilize the α -anion formed upon Michael addition, and slow down the polymerization due to its steric bulk. Additionally, being α -ketonic in the final compound, the silyl substituent could readily be removed by nucleophiles.

The silyl derivative **2** was prepared from (1-bromovinyl)-trimethylsilane (**10**) via the known²¹ allylic alcohol **11**, by a route inspired in the preparation of the Nazarov reagent **1**.^{1b,c} Dess-Martin oxidation of **11**, followed by acylation of the unstable acrolein derivative **12** with the enolate

(10) Benetti, S.; Carlo, S.; De Risi, C.; Pollini, G. P.; Veronese, A. C.; Zanirato, V. *Synlett* **2008**, 2609–2612.

(11) (a) For the double Michael addition of the Nazarov reagent to a nitroalkene, see: Albertini, E.; Barco, A.; Benetti, S.; Risi, C. D.; Pollini, G. P.; Romagnoli, R.; Zanirato, V. *Tetrahedron Lett.* **1994**, 35, 9297–9300. (b) However, see: Hoashi, Y.; Yabuta, T.; Yuan, P.; Miyabe, H.; Takemoto, Y. *Tetrahedron* **2006**, 62, 365–374.

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(16) Allin, S. M.; Thomas, C. I.; Doyle, K.; Elsegood, M. R. J. *J. Org. Chem.* **2005**, 70, 357–359.

(17) Pollet, P.; Gelin, S. *Synthesis* **1978**, 142–143.

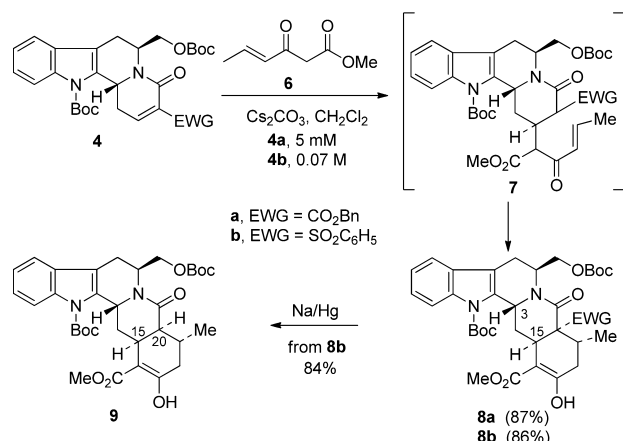
(18) When the reaction from **4b** was conducted for shorter times, mixtures of **8b** and the intermediate Michael adduct **7b** were formed.

(19) The *cis* D/E ring junction in **9** and **16** was evident from the positive NOE effect between 15-H and 20-H.

(20) Stork, G.; Ganem, B. *J. Am. Chem. Soc.* **1973**, 95, 6152–6153.

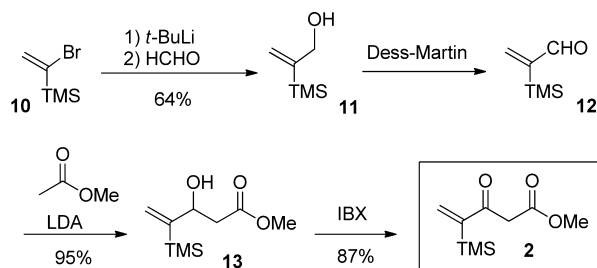
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Scheme 3. Double Michael Addition of Methyl 3-Oxo-4-hexenoate (**6**)



of methyl acetate, and IBX oxidation of the resulting β -hydroxy ester **13** gave **2** in 53% overall yield in four steps. This silylated Nazarov reagent was stable in storage at -20°C under nitrogen for several months.²²

Scheme 4. Preparation of the New Nazarov Reagent **2**



To our delight, reagent **2** satisfactorily reacted with unsaturated lactams **4a** and **4b** to give double Michael addition products, in which the trimethylsilyl group had undergone *in situ* protodesilylation.²³ Thus, treatment of **4a** with **2** under the reaction conditions outlined in Scheme 5 stereoselectively led to a single pentacycle **14a** in excellent yield. A subsequent removal of the Boc protecting group provided **15**. A similar reaction from **4b** afforded a diastereoisomeric mixture of pentacycles **14b** and **5b** (2:1 ratio; 64%),²⁴ the latter being stereoselectively converted to the

(22) Reagent **2** was stable enough to be purified by flash chromatography. Although TLC showed that no significant decomposition occurred on stirring a CH_2Cl_2 solution of **2** at 0°C for 2 h in the presence of Cs_2CO_3 , extensive polymerization was observed when the experiment was performed at rt.

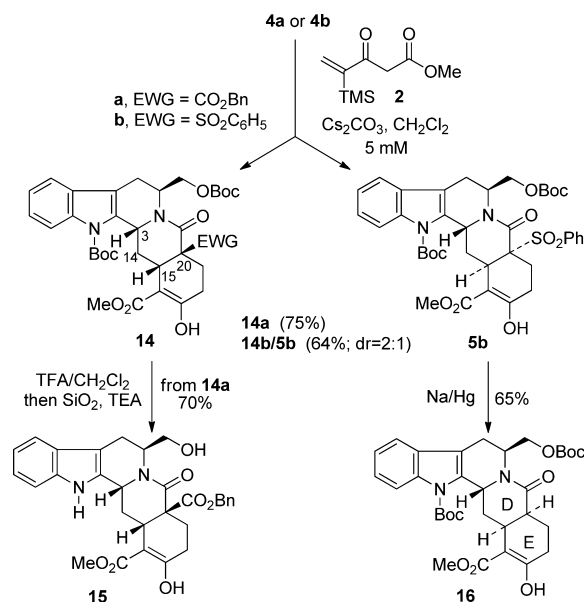
(23) In some runs from **4b**, a trimethylsilyl derivative was detected (NMR) during chromatographic purification of the crude reaction mixture.

(24) When the reaction was carried out at a higher concentration (0.1 M), an inversion of the stereochemistry was observed (**5b/14b** ratio 2:1; 62% yield). There are few cases in which concentration has a dramatic effect on the stereoselectivity of a reaction: Yang, F.; Zhu, Y.; Yu, B. *Chem. Commun.* **2012**, 48, 7097–7099 and ref cited therein.

epi-*allo*-yohimbinone derivative **16** by reductive removal of the activating benzenesulfonyl group.¹⁹

The absolute configuration of **5b** was unambiguously established by X-ray crystallography. In turn, the 3-H/15-H *cis* relationship in the isomers **14a** and **14b** (as well as in **19**; see Scheme 6) was deduced from the positive NOE effect between these protons. With these assignments taken into account, the NMR chemical shifts of the protons and carbons at the 3- and 14-positions were of diagnostic value to assign the C-3, C-15, and C-20 relative stereochemistry of the pentacyclic derivatives reported in this work (see tables in the Supporting Information).

Scheme 5. Double Michael Addition of the Nazarov Reagent Equivalent **2** to Unsaturated Lactams **4**



Similar satisfactory results were obtained in the reaction of the silylated Nazarov reagent **2** with unsaturated lactams **18** (Scheme 6), which lacks the *O*-Boc hydroxymethyl substituent, and **20** (Scheme 7), unprotected at the hydroxy function and indole nitrogen. The former was prepared from the known saturated lactam **17**²⁵ as outlined in Scheme 6, whereas the latter by was prepared by TFA treatment of the above lactam **4a**.

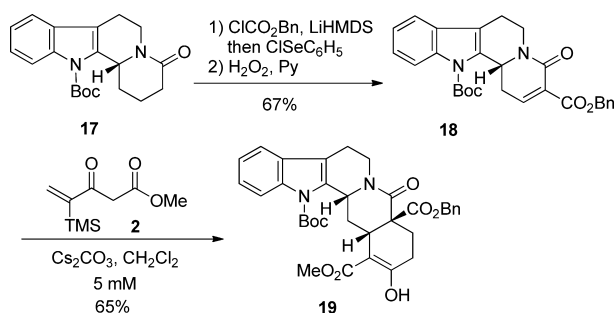
Somewhat surprisingly, whereas lactam **18** behaved like lactams **4**, stereoselectively leading to an all-*cis* pentacycle, **19**, the annulation from **20** took place with opposite facial selectivity, giving pentacycle **21** as the major product.²⁶

The stereochemical outcome of the double Michael additions deserves comment. The configuration of the C-15 stereocenter is generated in the initial attack of the Nazarov enolate, and it is known that conjugate addition to unsaturated indolo[2,3-*a*]quinolizidine lactams usually

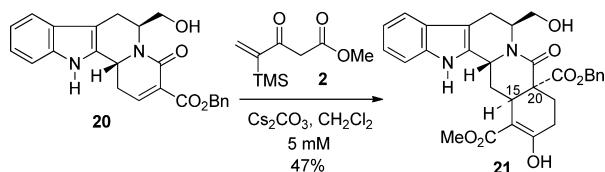
(25) Allin, S. M.; Khera, J. S.; Thomas, C. I.; Witherington, J.; Doyle, K.; Elsegood, M. R. J.; Edgar, M. *Tetrahedron Lett.* **2006**, 47, 1961–1964.

(26) Trace amounts of the 15,20-epimer were also formed.

Scheme 6. Double Michael Addition of the Nazarov Reagent Equivalent **2** to Unsaturated Lactam **18**



Scheme 7. Double Michael Addition of the Nazarov Reagent Equivalent **2** to Unsaturated Lactam **20**



leads to *trans* 3-H/15-H derivatives, although, for steric reasons, a reversal of the facial selectivity is observed when the indole nitrogen is Boc-protected.²⁷ On the other hand, the *cis* D/E ring junction²⁸ results from stereoelectronic control during the second Michael addition.²⁹

To further illustrate the synthetic usefulness of the silylated Nazarov reagent **2** as a synthetic equivalent of the original reagent **1**, we also studied Cs_2CO_3 -promoted double Michael annulations from cyclohexenones **22a** and **22b** (Scheme 8). Earlier attempts to perform the annulation

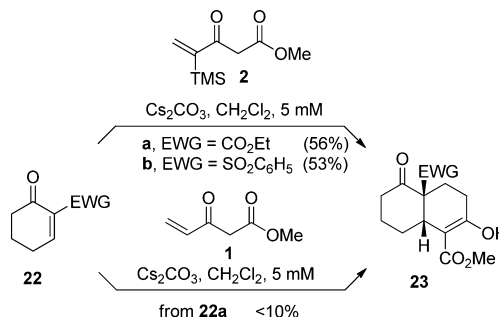
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(28) All pentacyclic derivatives prepared in this work were predominantly (or completely) enolic in solution, as expected for a *cis*-D/E ring junction in yohimbine-type systems: (a) Albright, J. D.; Goldman, L. *J. Org. Chem.* **1965**, 30, 1107–1110. (b) Brucher, F. V., Jr.; Vanderwerff, W. D.; Dreikorn, B. *J. Org. Chem.* **1972**, 37, 297–302.

(29) Berthiaume, G.; Lavallée, J.-F.; Deslongchamps, P. *Tetrahedron Lett.* **1986**, 45, 5451–5454.

of **22a** with **1** had only resulted in a very poor yield of **23a**. In contrast, the silylated derivative **2** satisfactorily gave the respective highly functionalized *cis*-decalins **23a**³⁰ and **23b** in acceptable yields.

Scheme 8. Double Michael Addition of the Nazarov Reagent Equivalent **2** to Enones **22**



In summary, we have developed a synthetic equivalent of the Nazarov reagent, the silyl derivative **2**, which is able to participate in Cs_2CO_3 -promoted double Michael annulations with α,β -unsaturated carbonyl compounds, avoiding the polymerization problem associated with the original Nazarov reagent. Starting from unsaturated indolo[2,3-*a*]-quinolizidine lactams, this silylated Nazarov reagent allows the straightforward construction of pentacyclic yohimbine-type systems.

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Supporting Information Available. Detailed experimental procedures for all new compounds, tables with ^1H and ^{13}C NMR chemical shifts of the pentacyclic derivatives, copies of ^1H and ^{13}C NMR spectra for selected compounds, and X-ray crystallographic information file (CIF) for **5b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(30) TLC of the crude reaction mixture showed the presence of a major compound and only minor amounts of the final product **23a**. After flash chromatography, *cis*-decalin **23a** was the only isolated compound, thus suggesting that protodesilylation mainly occurs during evaporation and purification.

The authors declare no competing financial interest.