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Sequential Acid/Base-Catalyzed Polycyclization of Tryptamine Derivatives. A Rapid Access to Büchi's Ketone§

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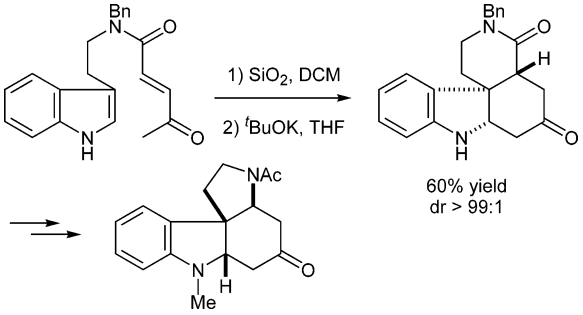
ABSTRACT



The development of an efficient and diastereoselective methodology that allows the rapid construction of the tetracyclic core of the *Aspidosperma* and *Strychnos* alkaloid families is decribed. Our approach relies upon two key steps: a sequential silica gel/potassium *tert*-butoxide polycyclization of a tryptamine precursor and a tandem oxidative decarboxylation/ring-closing reaction. The assembly of Büchi's ketone, a key intermediate in the synthesis of vindorosine, has been accomplished using this approach.

Indole alkaloids, such as strychnine **1**, vindoline **3**, and vindorosine **2**, have attracted considerable attention over the years, due to their enticing structures and biological activities. For decades, the construction of strychnine[1] has represented a formidable synthetic challenge that has only been met a few times. Vindoline, though possessing a simpler architectural framework,[2] is a key component in the preparation of the antitumor drugs vincristine and vinblastine.[3] These alkaloids share the same tetracyclic core **4**, known as the Büchi ketone ($R^2 = H$),[4] from which their complex structures could be elaborated. In this communication, we wish to report our results on the establishment of an efficient route toward **4** that hinges upon two key steps: an anionic polycyclization reaction and an oxidative ring-regression process (Figure 1).[5]

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§ Dedicated with deep respect and affection to Professor Martin E. Kuehne.

(1) (a) Pelletier, P. J.; Caventou, J. B. *Ann. Chim. Phys.* **1818**, *8*, 323. (b) Pelletier, P. J.; Caventou, J. B. *Ann. Chim. Phys.* **1819**, *810*, 142. (c) Openshaw, H. T.; Robinson, R. J. *Nature* **1946**, *157*, 438. (d) For a review of strychnine total syntheses until 2000, see: Bonjoch, J.; Sole, D. *Chem. Rev.* **2000**, *100*, 3455. (e) Ohshima, T.; Xu, Y.; Takita, R.; Shimizu, S.; Zhong, D.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14546. (f) Mori, M.; Nakanishi, M.; Kajishima, Da.; Sato, Y. *J. Am. Chem. Soc.* **2003**, *125*, 9801.

(2) (a) Gorman, M.; Neuss, N.; Biemann, K. *J. Am. Chem. Soc.* **1962**, *84*, 1058. (b) Moza, B. K.; Trojánek, J. *Collect. Czech. Chem. Commun.* **1963**, *28*, 1427.

(3) (a) Noble, R. L.; Beer, C. T.; Cutts, J. H. *Ann. N. Y. Acad. Sci.* **1958**, *76*, 882. (b) Svoboda, G. H.; Neuss, N.; Gorman, M. *J. Am. Pharm. Assoc. Sci. Ed.* **1959**, *48*, 659.

(4) (a) Buchi, G.; Matsumoto, K.; Nishimura, H. *J. Am. Chem. Soc.* **1971**, *93*, 3299. (b) Ando, M.; Buchi, G.; Ohnuma, T. *J. Am. Chem. Soc.* **1975**, *97*, 6880.

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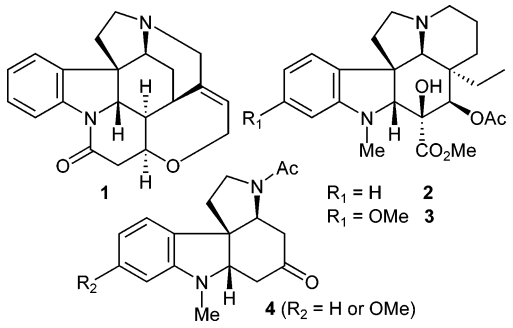
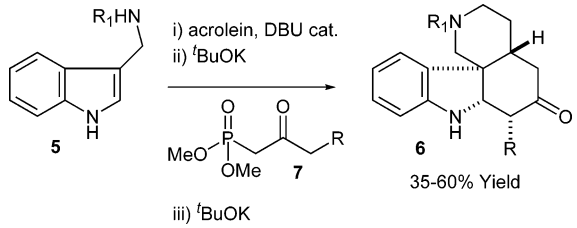


Figure 1.

As part of our ongoing efforts directed toward the preparation of highly functionalized tetracyclic indolino-compounds, akin to the core of various natural products, we have developed a novel, one-pot, three-component anionic polycyclization reaction, depicted in Scheme 1.[6] This process

Scheme 1

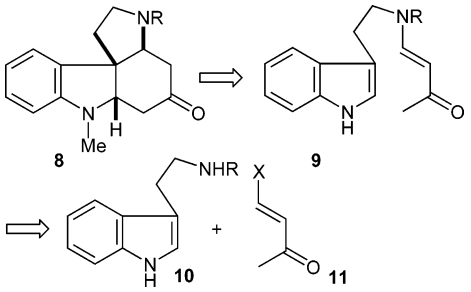


involves the Michael addition of gramine derivative **5** to acrolein, followed by a Horner−Emmons condensation and an intramolecular anionic polycyclization sequence.

Our retrosynthetic analysis of **8**, based upon this anionic polycyclization retron, is depicted in Scheme 2. Thus, the tetracyclic ketone **8** could be derived from an appropriate enaminone precursor **9**, which would in turn originate from the condensation of a protected tryptamine **10** and a Michael acceptor bearing a suitable leaving group at the β-position **11**.

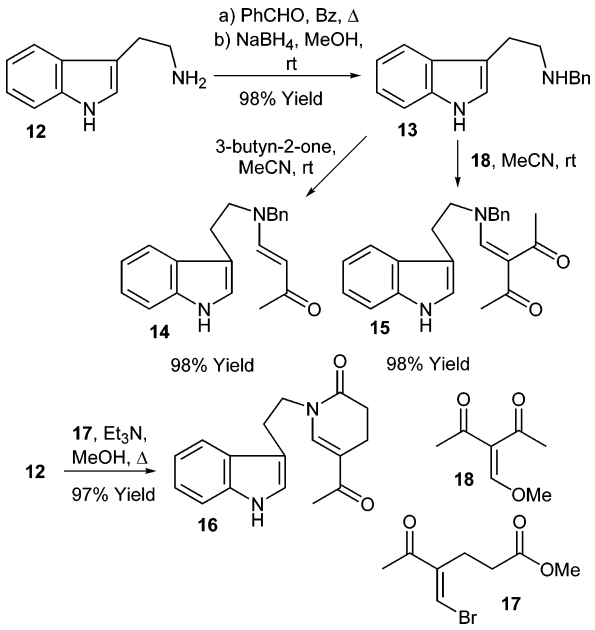
Our approach toward **8** began with the condensation of *N*-benzyltryptamine **13**, prepared almost quantitatively from tryptamine **12**,[7] with 3-butyn-2-one leading to **14** in excellent

Scheme 2



overall yields. To prepare more activated enaminones, the same coupling reaction was performed with 3-methoxy-methylene-2,4-pentanedione **18**, affording in 98% yield the corresponding di-keto derivative **15**. Finally, the construction of the cyclic precursor **16**, which could directly lead to a pentacyclic adduct by anionic polycyclization, was accomplished using the ϵ-bromoester **17**[8] in 97% yield (Scheme 3).

Scheme 3



With a ready access to these three key precursors, we next turned our attention to the crucial anionic polycyclization cascade.[9] Disappointingly, no reaction was observed under a wide range of conditions, including Brønsted bases, combination of Brønsted bases and Lewis acids or ambident

(5) For alternative strategies for the synthesis of vindoline and vindorosine, see: (a) Ban, Y.; Sekine, Y.; Oishi, T. *Tetrahedron Lett.* **1978**, *2*, 151. (b) Takano, S.; Shishido, K.; Matsuzaka, J.; Sato, M.; Ogasawara, K. *Heterocycles* **1979**, *13*, 307. (c) Veenstra, S. J.; Speckamp, W. N. *J. Am. Chem. Soc.* **1981**, *103*, 4645. (d) Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y. *J. Org. Chem.* **1985**, *50*, 961. (e) Danieli, B.; Lesma, G.; Palmisano, G.; Riva, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 155. (f) Feldman, P. L.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 1603. (g) Kuehne, M. E.; Podhorez, D. E.; Mulamba, T.; Bornmann, W. G. *J. Org. Chem.* **1987**, *52*, 347. (h) Winkler, J. D.; Scott, R. D.; Williard, P. G. *J. Am. Chem. Soc.* **1990**, *112*, 9871. (i) Kobayashi, S.; Ueda, T.; Fukuyama, T. *Synlett* **2000**, *6*, 883. (j) Zhou, S.; Bommezijn, S.; Murphy, J. A. *Org. Lett.* **2002**, *4*, 443. (k) Guo, Z.; Schultz, A. G. *Tetrahedron Lett.* **2004**, *45*, 919.

(6) Turet, L.; Markó, I. E.; Tinant, B.; Declercq, J.-P.; Touillaux, R. *Tetrahedron Lett.* **2002**, *43*, 6591.

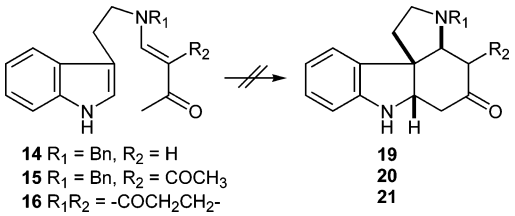
(7) Boumendjel, A.; Nuzillard, J.-M.; Massiot, G. *Tetrahedron Lett.* **1999**, *40*, 9033.

(8) Kalaus, G.; Greiner, I.; Kajtár-Peredy, M.; Eles, J.; Szabó, L.; Szabó, P.; Szántay, C. *Tetrahedron* **2002**, *58*, 8921.

(9) For some selected examples of anionic cyclisations, see ref 1 and references therein and (a) Markó, I. E.; Southern, J. M.; Adams, H. *Tetrahedron Lett.* **1992**, *33*, 4657. (b) Solberghe, G.; Markó, I. E. *Tetrahedron Lett.* **2002**, *43*, 5061.

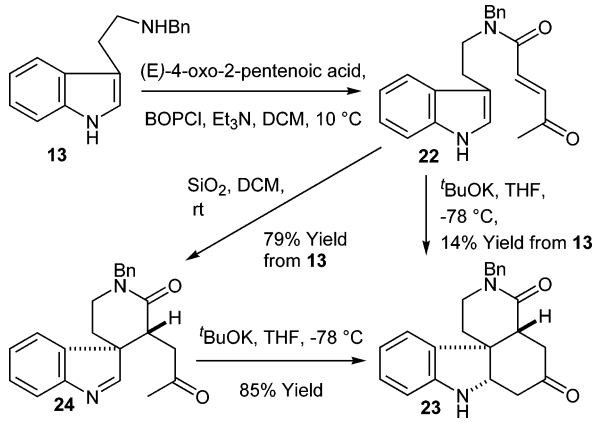
reagents combining these two properties, and the starting materials were recovered. Using more forcing conditions only resulted in extensive decomposition. It thus transpires that the poor electrophilicity of the enaminone function hampers the addition of the indolinyl anion to the conjugated system (Scheme 4).

Scheme 4



To circumvent this problem, a more potent Michael acceptor is required. It was decided to introduce an electron-withdrawing group between the nitrogen atom and the enone system and **22** became our next objective. Tryptamine derivative **22** was efficiently prepared by coupling *N*-benzyltryptamine **13** with (*E*)-4-oxo-2-pentenoic acid, in the presence of BOP-Cl.[10] Unfortunately, attempted purification of **22** using classical methods repeatedly failed and extensive degradation was observed in all cases. However, when crude **22** was treated directly with ^{t}BuOK in THF, at −78 °C, the corresponding polycyclic adduct **23** could be isolated for the first time, as a single diastereoisomer, albeit in rather modest yield (Scheme 5). It appears that the exacerbated reactivity

Scheme 5



of **22** now leads, under the usual basic conditions required for the polycyclization, to the formation of numerous undesired side products. Therefore, milder reaction conditions were explored. Unexpectedly, when treated overnight with silica gel in CH_2Cl_2, the unstable enone **22** was smoothly converted into the unique imino-spiro compound **24** in a good overall yield of 79%. Finally, base-catalyzed imino-aldol cyclization proceeded at −78 °C and afforded the long-sought-after tetracycle **23**, in excellent yield and as a single diastereoisomer. The high reactivity of compound **22** was thus bypassed using an efficient two-step sequence, involving a silica gel mediated cyclization followed by an anionic ring closure[11] (Scheme 5).

The structure of the spirocyclic adduct **24** was determined by 2D-NMR experiments and unambiguously established by single-crystal X-ray diffraction analysis. The piperidine ring system adopts a halfchair-like conformation in which the chain bearing the ketone function occupies an equatorial position *anti* to the imine portion of the indolenine nucleus (Figure 2).

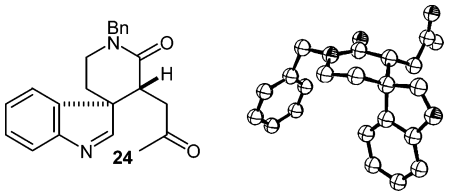


Figure 2.

Although readily available in only two operations from tryptamine **13**, tetracycle **23** possesses one carbon too many and a ring contraction is required to reach the core of the *Aspidosperma* and *Strychnos* alkaloids. It was envisioned that hydrolysis of the amide bond of **23**, followed by an oxidative decarboxylation, would afford the desired product **4**. However, the robust nature of the *N*-benzyl amide precluded its hydrolysis and its conversion into the *N*-Boc derivative became mandatory. Initially, the indolino nitrogen of **23** was methylated using excess methyl iodide and potassium carbonate in refluxing acetonitrile. Although several hydrogenation conditions failed to deprotect the *N*-benzyl amide **25**, sodium, in a mixture of ammonia and tetrahydrofuran, selectively cleaved the benzyl group. Amine **26** was then transformed into the corresponding Boc-protected amide **27** in excellent overall yield. According to a procedure described by Potier et al.,[12] the *N*-Boc amide **27** opened smoothly, when treated with an aqueous 1 M solution of lithium hydroxide, affording the free carboxylic acid **28** in 87% yield (Scheme 6).

At this juncture, all that remained to complete the synthesis of the tetracyclic core of the *Aspidosperma* and *Strychnos* alkaloid families was a tandem oxidative decarboxylation−Michael addition reaction. The oxidative removal of a carboxylic acid can be accomplished using various procedures, including lead chemistry developed by Kochi,[13] radical

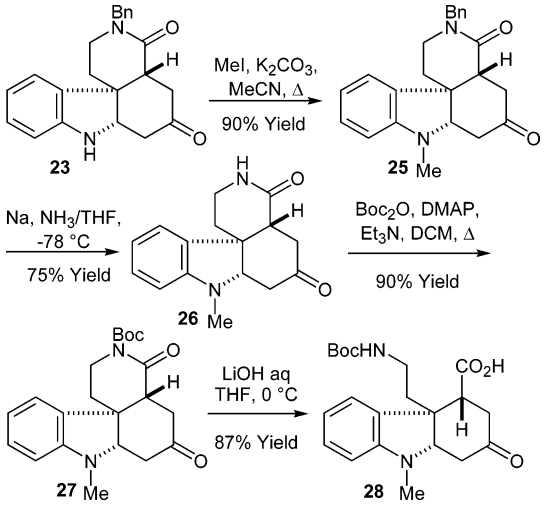
(10) Diago-Messeguer, J.; Palomo-Coll, A. L.; Fernández-Lizarbe, J. R.; Zugaza-Bilbao, A. *Synthesis* **1980**, 547.

(11) This sequence can also be performed as a one-pot operation by directly adding an excess of ^{t}BuOK to the heterogeneous mixture (60% yield).

(12) (a) Sagnard, I.; Sasaki, N. A.; Chiaroni, A.; Riche, C.; Potier, P. *Tetrahedron Lett.* **1995**, *36*, 3149.

(13) (a) Kochi, J. K. *J. Am. Chem. Soc.* **1965**, *87*, 2500. (b) Sheldon, R. A.; Kochi, J. K. *Org. React.* **1972**, *19*, 279.

Scheme 6



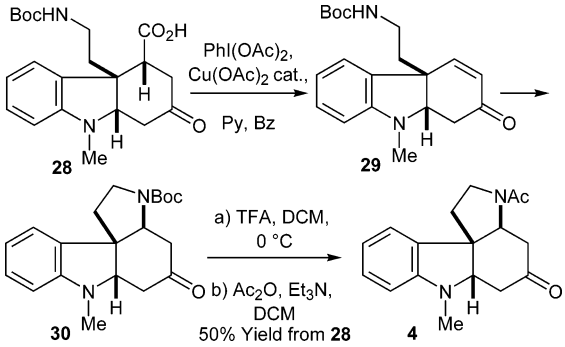
decomposition of thiohydroxamic derivatives,[14] or Pd^{II}-catalyzed decarboxylation of pivaloyl mixed anhydrides.[15] While the last two methods only led to regeneration of our tetracyclic amide **27**, the use of $Pb(OAc)_4$ resulted in complete degradation of the starting material. We believe that the two oxidizible nitrogen atoms present in **28** interfere with the normal oxidative-decarboxylation pathway, leading to the generation of numerous byproducts. Fortunately, modified Kochi's conditions, initially introduced by Suarez et al. and employing hypervalent iodine-based reagent instead of lead tetraacetate,[16] afforded a crude product containing mostly the desired compound **30**, presumably through the intermediacy of enone **29**. Crude product **30** was immediatly converted, in two steps, into Büchi's ketone **4**, identical in all respects to previously reported material (50% overall yield).[17] (Scheme 7).

(14) Barton, D. K.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.

(15) Gooben, L. J.; Rodríguez, N. *Chem. Commun.* **2004**, 724.

(16) Concepcion, J. I.; Francisco, C. G.; Freire, R.; Hernandez, R.; Salazar, J. A.; Suarez, E. *J. Org. Chem.* **1986**, *51*, 402.

Scheme 7



In summary, we have developed an efficient and diastereoselective methodology that enables the rapid construction of the tetracyclic indolino-derivative **30**, the core of the *Aspidosperma* and *Strychnos* alkaloid families (8 steps, 17% overall yield). This approach hinges upon two key steps: a one-pot silica gel/^{t}BuOK polycyclization sequence and an oxidative decarboxylation−Michael addition reaction. Current efforts are now directed toward expending the scope of this novel methodology, developing an enantioselective version, and applying it to the synthesis of strychnine and vindoline.

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Supporting Information Available: Experimental procedures and full spectroscopic data, including spectra copies, for all new compounds; crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) We are grateful to Prof. J. D. Winkler for kindly providing us wih spectroscopic data for this compound.[5j]