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Biogenetically Inspired Enantioselective Approach to Indolo[2,3-*a*]- and Benzo[*a*]quinolizidine Alkaloids from a Synthetic Equivalent of Secologanin

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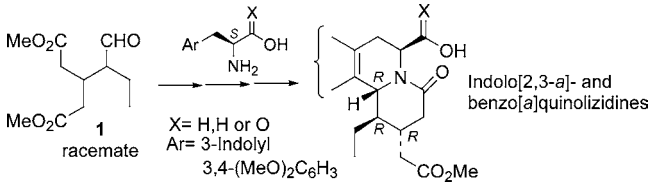
ABSTRACT



Racemic oxodiester 1 undergoes stereoselective cyclocondensation with (*S*)-tryptophanol, (*S*)-(3,4-dimethoxyphenyl)alaninol, or the corresponding amino acids, in a process involving a tandem dynamic kinetic resolution/desymmetrization of diastereotopic groups, to give bicyclic lactams, which are cyclized to substituted indolo[2,3-*a*]- and benzo[*a*]quinolizidines.

Secologanin (Figure 1) is a secoiridoid glucoside of extraordinary significance because it is a key intermediate in the biosynthesis of monoterpenoid indole alkaloids as well as of emetine and related benzo[*a*]quinolizidine alkaloids,[1] many of them possessing considerable pharmacological and therapeutic interest.[2] A condensation of secologanin with either tryptamine (or tryptophan) or dopamine constitutes the initial step of the biosynthesis of these natural products.

The pivotal role of secologanin in alkaloid biosynthesis has stimulated the development of biomimetic syntheses of alkaloids using this compound as the starting material.[3,4]

We present here an efficient synthesis of racemic aldehyde diester **1**, which can be envisaged as a synthetic equivalent

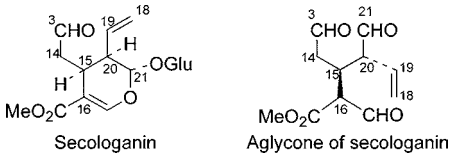


Figure 1. Secologanin and its aglycone.

of secologanin,[5] and its use in cyclocondensation reactions with chiral nonracemic amino alcohols **9a** and **17a** as well

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(1) Stöckigt, J.; Ruppert, M. In *Comprehensive Natural Products*; Barton, D., Nakanishi, K., Eds.; Elsevier: New York, 1999; Vol. 4, pp 109−138.

(2) (a) Neuss, N. In *Indole and Biogenetically Related Alkaloids*; Phillipson, J. D., Zenk, M. H., Eds.; Academic Press: London, 1980; Chapter 17. (b) Dewick, P. *Medicinal Natural Products. A Biosynthetic Approach*; Wiley: Chichester, 2002.

(3) For reviews, see: (a) Brown, R. T. In *The Chemistry and Biology of Isoquinoline Alkaloids*; Phillipson, J. D., Roberts, M. F., Zenk, M. H., Eds.; Springer-Verlag: Berlin, 1985; pp 204−212. (b) Brown, R. T. In *Indole and Biogenetically Related Alkaloids*; Phillipson, J. D., Zenk, M. H., Eds.; Academic Press: London, 1980; Chapter 9.

(4) For a recent review on biomimetic synthesis of alkaloids, see: Scholz, U.; Winterfeldt, E. *Nat. Prod. Rep*. **2000**, *17*, 349.

(5) For the synthesis of an analogue of secologanin and its use in the total synthesis of monoterpenoid isoquinoline alkaloids, see: Brown, R. T.; Jones, M. F. *Tetrahedron Lett*. **1984**, *25*, 3127.

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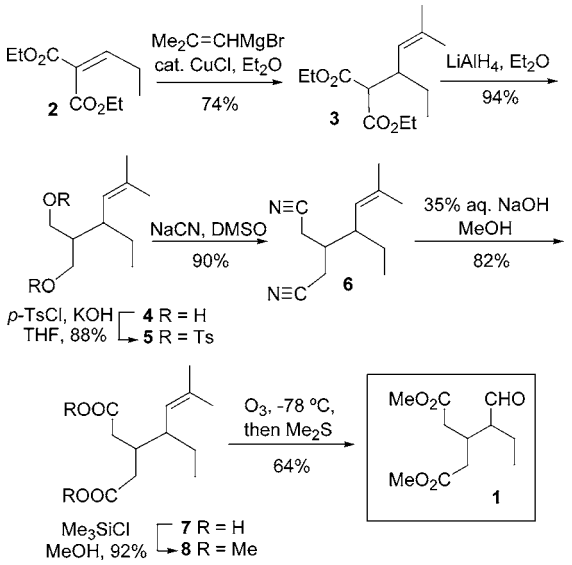
Scheme 1. Synthesis of the Synthetic Equivalent of Secologanin

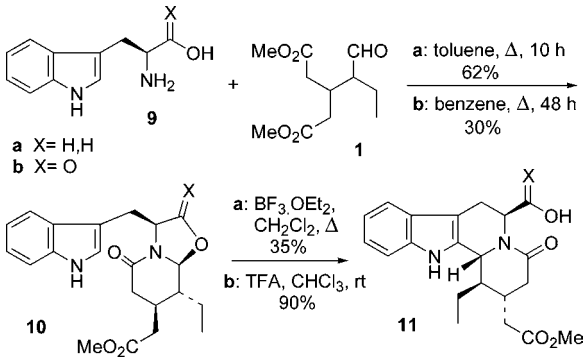


as amino acids (*S*)-tryptophan (**9b**) and (*S*)-(3,4-dimethoxyphenyl)alanine (**17b**), ultimately leading to enantiopure indolo[2,3-*a*]- and benzo[*a*]quinolizidines.

The synthesis of target **1**, depicted in Scheme 1, involves the conjugate addition of 2-methyl-1-propenylmagnesium bromide to unsaturated diester **2**, a bis-homologation of the resulting diester **3** to diester **8** via diol **4**, tosylate **5**, and dinitrile **6**, and finally reductive ozonolysis[6] of the alkene moiety. The synthesis can be satisfactorily conducted at a 50−100 g scale, and most of the steps take place in excellent yield.

On the basis of our experience in related cyclocondensations using phenylglycinol or other amino alcohols as the source of chirality,[7] we expected that, although synthon **1** is a racemate, it would undergo a stereoselective cyclocondensation with (*S*)-tryptophanol (**9a**) in a process involving a dynamic kinetic resolution,[8] with epimerization of the configurationally labile stereocenter α to the carbonyl group and simultaneous desymmetrization of the two diastereotopic acetate chains.[9] Advantageously with respect to these cyclocondensations, tryptophanol not only would act as a chiral inductor but also would be incorporated in the target final products.[10] In the event, refluxing a toluene solution of tryptophanol (**9a**) and **1** under Dean−Stark conditions gave enantiopure lactam **10a**[11] in 62% yield (Scheme 2). Three stereogenic centers with a well-defined configuration have been generated in a single synthetic step. Only minor amounts (∼10%) of other diastereoisomers were formed.

Scheme 2. Enantioselective Entry to Substituted Indolo[2,3-*a*]quinolizidines



The observed stereoselectivity can be explained by considering that the initially formed diastereomeric imines are in equilibrium via an enamine and that the final irreversible lactamization of the mixture of equilibrating oxazolidines occurs faster via a transition state in which all the substituents in the incipient chairlike six-membered lactam are in an equatorial disposition (Figure 2).

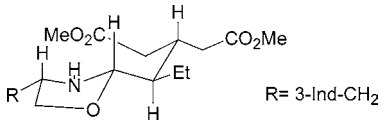


Figure 2. Stereoselective lactamization to **10a**.

A subsequent intramolecular $BF_3{\cdot}OEt_2$-promoted α-aminoalkylation on the indole 2-position, taking advantage of the masked *N*-acyliminium moiety present in the bicyclic lactam **10a**, led to the indolo[2,3-*a*]quinolizidine derivative **11a**[12] in 35% yield.

Although cyclocondensation reactions of γ- and δ-oxoesters with chiral nonracemic amino alcohols have received considerable attention,[13] since the resulting lactams have proven to be versatile building blocks for the enantioselective synthesis of nitrogen-containing derivatives,[14] to our knowledge there is no precedent for the use of amino acids in similar cyclocondensations. For this reason, we decided to investigate the cyclocondensation of (*S*)-tryptophan (**9b**) with

(6) For related ozonolysis, see: Cartier, D.; Lévy, J. *Tetrahedron* **1990**, *46*, 5295.

(7) (a) Amat, M.; Cantó, M.; Llor, N.; Ponzo, V.; Pérez, M.; Bosch, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 335. (b) Amat, M.; Bassas, O.; Pericàs, M. A.; Pastó, M.; Bosch, J. *Chem. Commun.* **2005**, 1327.

(8) For a recent review, see: Pellissier, H. *Tetrahedron* **2003**, *59*, 8291.

(9) For reviews, see: (a) Danieli, B.; Lesma, G.; Passarella, D.; Riva, S. In *Advances in the Use of Synthons in Organic Chemistry*; Dondoni, A., Ed.; JAI Press: London, 1993; Vol. 1, pp 143−219. (b) Schoffers, E.; Golebiowski, A.; Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769. (c) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765. (d) Danieli, B.; Lesma, G.; Passarella, D.; Silvani, A. *Curr. Org. Chem.* **2000**, *4*, 231.

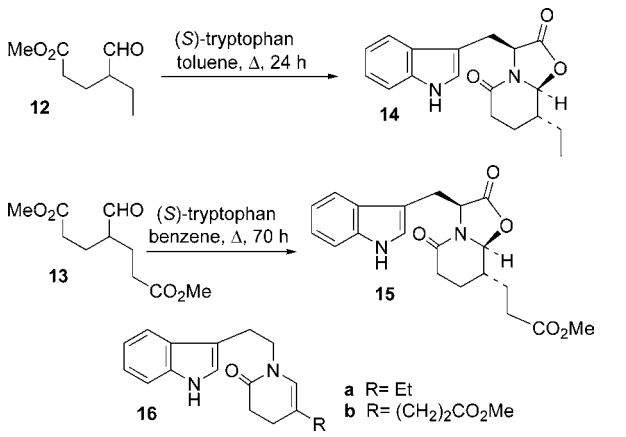
(10) For the use of tryptophanol in a cyclocondensation reaction with a simple δ-oxoester, see: Allin, S. M.; Thomas, C. I.; Doyle, K.; Elsegood, M. R. J. *J. Org. Chem.* **2005**, *70*, 357.

(11) Stereochemistry of **10a** was assigned taking into account: (i) the preferential formation of cis H_3-H_{8a} oxazolidine isomers in related cyclocondensations from aldehydes;[7,10] (ii) the H_8-H_{8a} *J* value (8.4 Hz), indicating of a trans relationship; and (iii) the absolute configuration of the cyclized product **11a** (see below).

(12) Absolute configuration of lactams **10b**, **11a**, and **19a** was unambiguously established by X-ray crystallography (see Supporting Information).

several δ-oxoesters and δ-oxodiesters, including the secologanin equivalent **1**. Thus, racemic oxoester **12**[15] and prochiral oxodiester **13**[7a] were converted to the corresponding enantiopure lactams **14** and **15** by treatment with (*S*)-tryptophan in refluxing toluene, although the yields were quite moderate (35% based on consumed aldehyde for **14**) as a consequence of the insolubility of the starting amino acid and a competitive decarboxylation process (Scheme 3). In both cases, the

Scheme 3. Cyclocondensation Reactions Using the Amino Acid (*S*)-Tryptophan

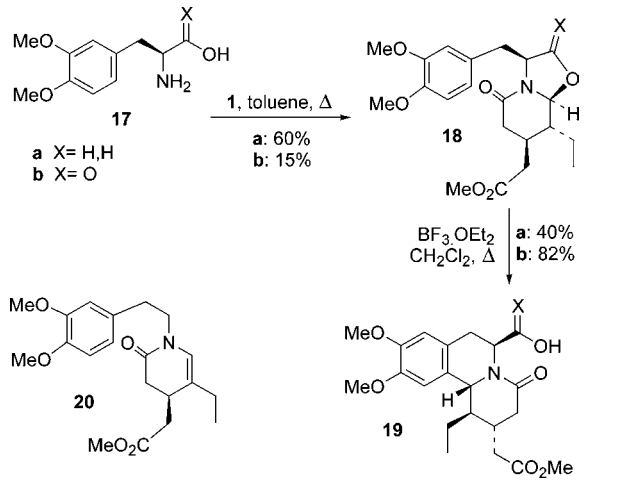


respective enamides **16a** or **16b**, resulting from decarboxylation of the initially formed oxazolidinones,[16] were isolated to a considerable extent (30−50%). The yield of the process was improved to 65% (77% based on consumed aldehyde; 2:1 mixture of **15** and its 8,8a-diastereomer), and the undesired formation of enamide was reduced (∼5%), when the cyclocondensation of **13** was carried out in refluxing benzene. Similarly, cyclocondensation of (*S*)-tryptophan with **1** in refluxing benzene took place in 42% yield to give a mixture of lactams, from which enantiopure piperidone **10b**[12] was isolated in 30% yield. In this series, cyclization to the corresponding indolo[2,3-*a*]quinolizidine **11b** occurred smoothly in excellent yield (90%) by treatment of **10b** with TFA at room temperature.

The secologanin equivalent synthon **1** was also satisfactorily used to provide an enantioselective entry to substituted benzo[*a*]quinolizidine derivatives.[17]

Cyclocondensation of **1** with dimethoxyphenylalaninol **17a**[18] in refluxing toluene under Dean−Stark conditions took place in excellent yield (80%) to give a mixture of stereoisomeric lactams, from which the enantiopure isomer **18a** was isolated in 60% yield. A subsequent cyclization of **18a** with $BF_3{\cdot}OEt_2$ led to benzo[*a*]quinolizidine **19a**[12] in 40% yield (Scheme 4).

Scheme 4. Enantioselective Entry to Substituted Benzo[*a*]quinolizidines



As observed in the above cyclocondensations with (*S*)-tryptophan, reaction of the amino acid **17b** with oxodiester **1** was less efficient, and the expected bicyclic lactam **18b** was isolated in low yield (∼15%; 30% based on recovered aldehyde), enamide **20** being the major product (42%) when the reaction was carried out in refluxing toluene. Cyclization of **18b** with $BF_3{\cdot}OEt_2$ provided benzo[*a*]quinolizidine **19b** in 82% yield.

The straightforward route to substituted indolo[2,3-*a*]- and benzo[*a*]quinolizidines reported herein significantly expands the potential of amino alcohol-derived bicyclic lactams as chiral synthons for the enantioselective construction of complex piperidine-containing derivatives. The amino alcohol (or amino acid) used as the chiral inductor in the cyclocondensation reaction not only constitutes the source of chirality but also is used to assemble the final target polycyclic products. In conjunction with this, the use of an appropriately substituted racemic δ-oxodiester

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(15) Norman, M. H.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 3370.

(16) (a) Grigg, R.; Idle, J.; McMeekin, P.; Vipond, D. *J. Chem. Soc., Chem. Commun.* **1987**, 49. (b) Tsuge, O.; Kanemasa, S.; Ohe, M.; Takenaka, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4079.

(17) For a recent review on the asymmetric synthesis of isoquinoline alkaloids, see: Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341.

(18) For the use of **17a** in a cyclocondensation reaction with a simple δ-oxoester, see: Allin, S. M.; Vaidya, D. G.; James, S. L.; Allard, J. E.; Smith, T. A. D.; Mckee, V.; Martin, W. P. *Tetrahedron Lett.* **2002**, *43*, 3661.

allows the direct generation of enantiopure lactams that already incorporate carbon substituents on the heterocyclic ring, in a process involving a tandem dynamic kinetic resolution−desymmetrization of diastereotopic acetate chains.

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Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra of compounds **1**, **10**, **11**, **14**, **15**, **18**, and **19**; complete X-ray crystallographic data for **10b**, **11a**, and **19a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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