Recent Progress in Efficient Syntheses of Amaryllidaceae and Morphine Alkaloids

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1. Introduction.

Morphine (**1**) and pancratistatin (**2**), as well as some of its congeners such as 7-deoxypancratistatin (**3**), narciclasine (**4**), and lycoricidine (**5**), can all be viewed as derivatives of highly oxygenated biphenyls, as indicated in Figure 1.

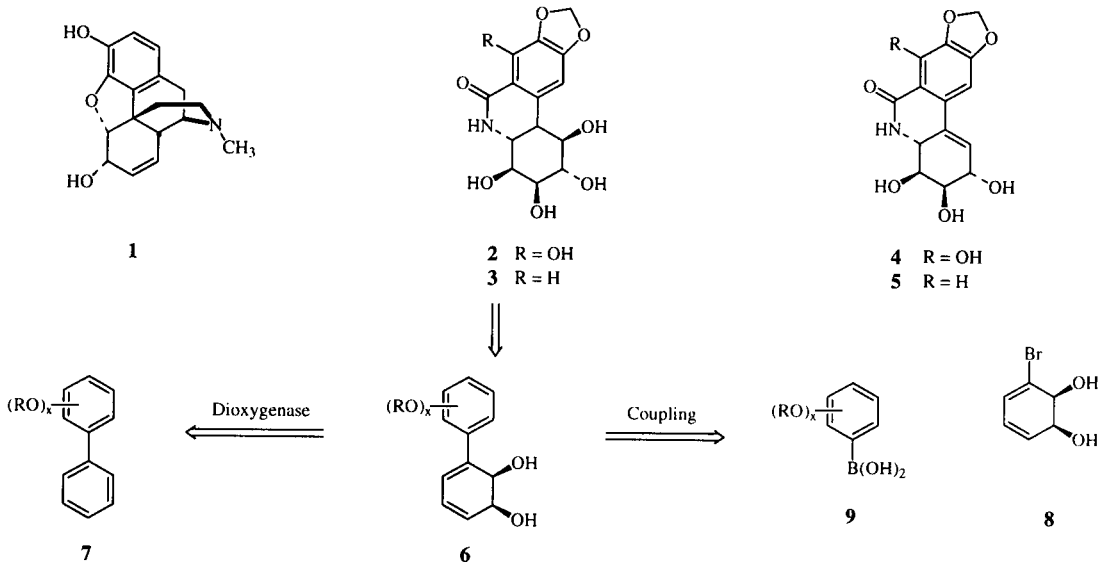


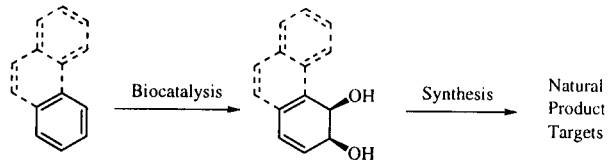
Figure 1. Design Strategies for Alkaloid Synthesis.

The common substructure unit lends itself to consideration of biocatalytic design in which homochiral biphenyl derivatives such as **6** are generated either by enzymatic dihydroxylation of biphenyls with organisms expressing biphenyl or toluene dioxygenase or by Suzuki coupling of similarly produced diol **8** with appropriate boronic acids **9**.

The design depends on the established technology of generating the required homochiral diene diols by whole-cell fermentation of arenes with *E. coli* JM109(pDTG601A)—a recombinant organism developed by Gibson [1]. Over the last 10 years or so, our laboratory has successfully implemented chemoenzymatic strategy for synthesis of many complex natural products [2]. In this manuscript, we provide a progress report on the multi-generation effort toward both morphine and Amaryllidaceae alkaloids.

2. Discussion.

Enzymatic dihydroxylation of aromatics, portrayed in Figure 2, provides numerous synthons for asymmetric synthesis [3].The three classes of aromatics are substrates for three related enzymes, all available in either blocked mutants or recombinant strains. A recent review [3] summarizes the synthetic efforts that build on this remarkable transformation, unparalleled in traditional synthesis, termed recently a "Birch-type oxidation" [4]. The application of this technology to the synthesis of the title alkaloids seemed clear once the placement of the *cis*-diol has been recognized in the target.



Single ring aromatics: toluene dioxygenase (TDO)
Fused aromatics: naphthalene dioxygenase (NDO)
Biphenyl aromatics: biphenyl dioxygenase (BPO)

Figure 2. Enzymatic Dihydroxylation of Aromatics.

2.1 Amaryllidaceae Alkaloids.

Our first venture into the synthesis of this class of compounds provided lycoricidine in nine steps from bromobenzene, as outlined in Figure 3 [5].

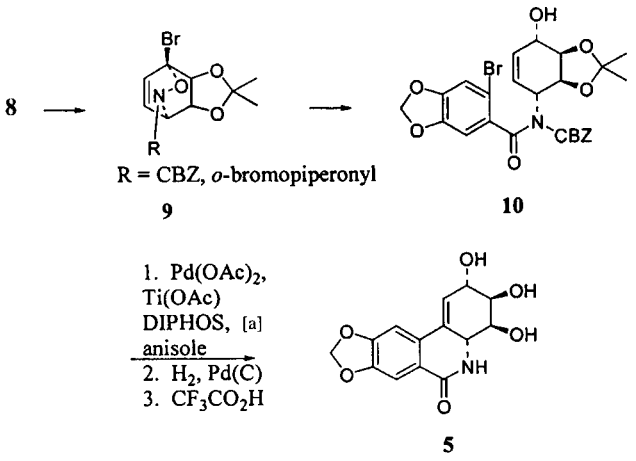


Figure 3. Synthesis of Lycoricidine; [a] DIPHOS: 1,2-Bis(diphenylphosphino)ethane.

At first, we had hoped to hydrate the styrene bond in lycoricidine to the more important alkaloid, pancratistatin. However, this transformation was unsuccessful, and, in the first asymmetric synthesis of **2**, we took advantage of the aziridine opening shown in Figure 4 to attain the alkaloid [6,7].

porating the incipient amide carbonyl into the aziridine activating group as a carbamate and employing Banwell's conditions [8] for the ring closure, as shown in Figure 5.

7-Deoxypancratistatin [9] (as well as *ent*-7-deoxypancratistatin [10]) has been made with considerable improvements in the overall synthetic sequence. The last member

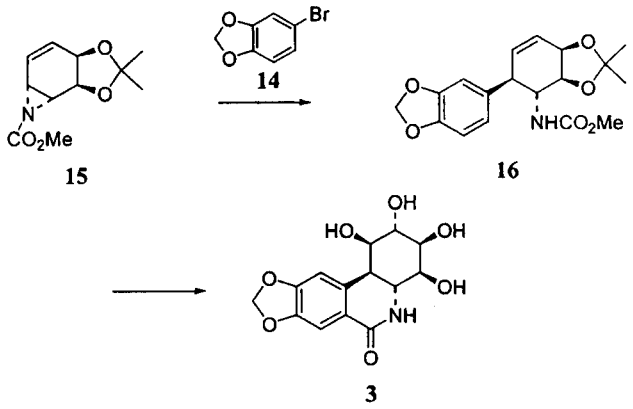


Figure 5. Second Generation Synthesis of (+)-7-Deoxypancratistatin.

of this series, narciclasine, was prepared as shown in Figure 6 by coupling a vinyl bromide to the oxygenated boronic acid [11]. Following the synthesis of all four alkaloids, we returned to the pancratistatin synthesis to make further improvements. To this end, a new intramolecular aziridine opening strategy has been implemented in the

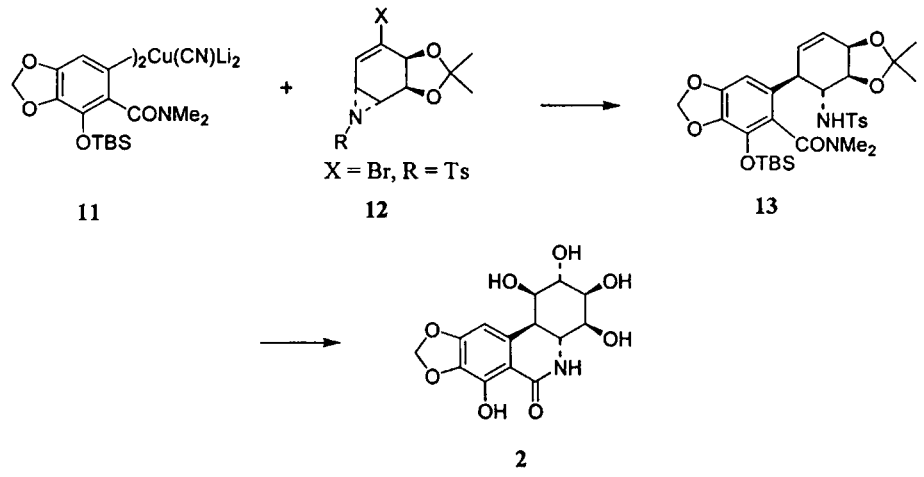


Figure 4. First Asymmetric Synthesis of Pancratistatin; TBS: *t*-Butyldimethylsilyl.

The thirteen-step synthesis was plagued with many functional transformations related to the robust nature of both benzamide and tosylamide groups. In the second-generation attempt, these problems were solved by incorporation of the simpler 7-deoxy derivative as shown in Figure 7 [12]. This latest result will enable a more efficient approach to pancratistatin (**2**) in our quest for a practical route to this alkaloid.

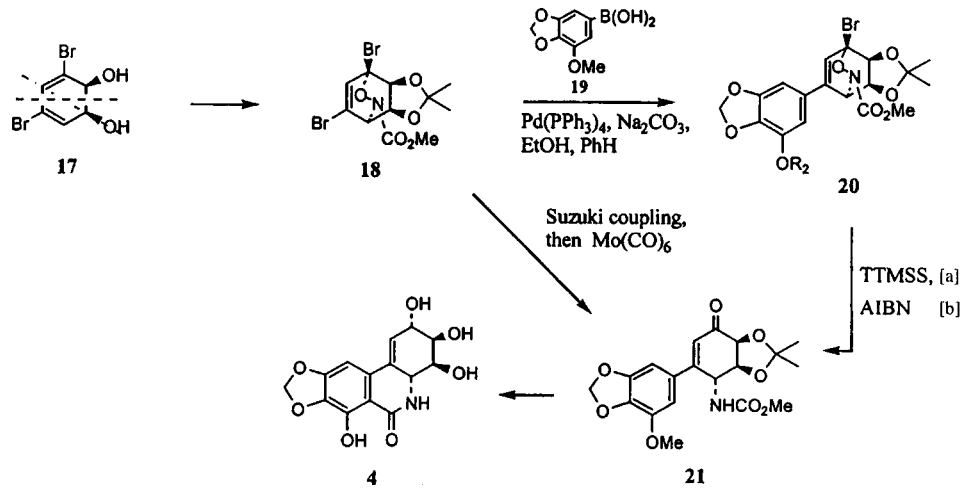


Figure 6. Synthesis of Narciclasine; [a] TTMSS: Tris(trimethylsilyl)silane; [b] AIBN: 2,2'-Azobisisobutyronitrile.

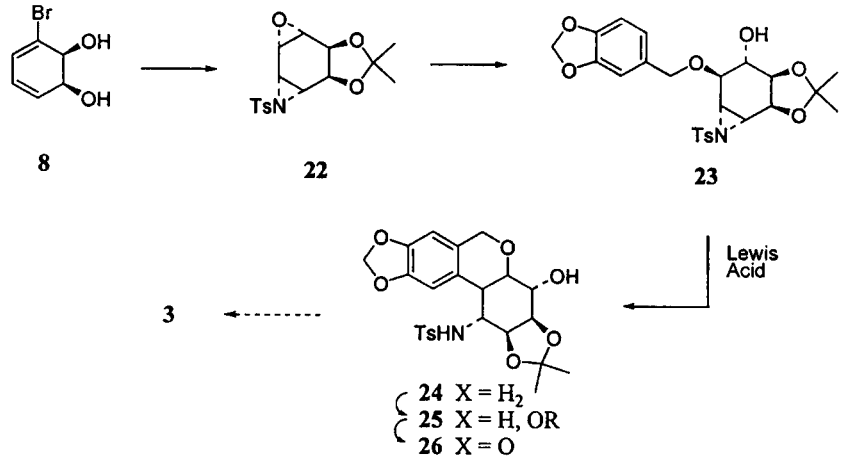


Figure 7. New Intramolecular Aziridine Opening Strategy.

2.2 Morphine Alkaloids.

The first attempt at a biocatalytic synthesis of morphine involved the tandem radical cyclization shown in Figure 8 [13,14]. The desired pentacyclic compound **29** was formed in a low yield and with poor stereospecificity. A partial solution to this drawback was realized by performing the cyclization in separate steps, as shown, and this approach ultimately led to *ent*-morphinan **31**. Additional improvements in producing the oxygenated octahydroquinolines **33** were realized through the judicious use of an acyliminium type closure, which resulted in excellent control of the C-9 center in both enantiomeric series of the alkaloid [15].

An unrelated approach to morphine took advantage of the chelated enolate Claisen rearrangement reported by Kazmaier [16], in which zinc enolates of glycine produced stereospecifically substituted amino acid derivatives [17]; in this fashion, the amino acid **36** was attained. Current research activities center around the methods for C10-C11 closure and the ethylamine bridge construction.

The third approach to morphine involves the use of intramolecular Diels-Alder reaction. In a model system, this approach leads to the correct setting of all five stereocenters [18].

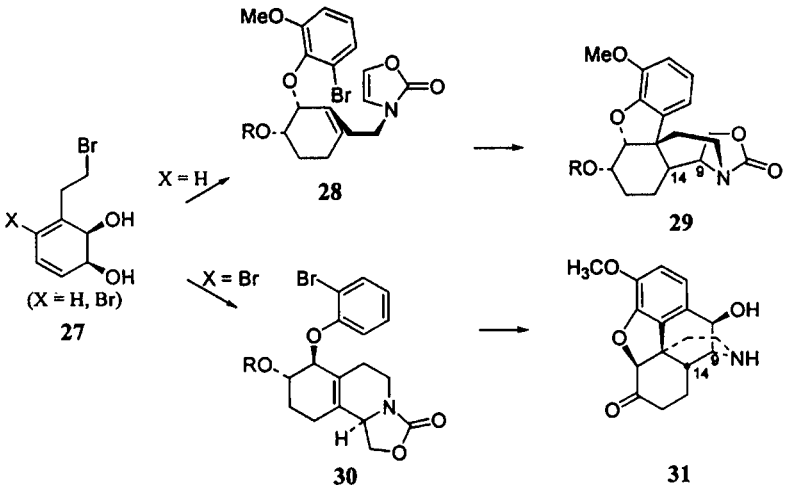


Figure 8. Tandem and Stepwise Cyclization Approach to Morphine.

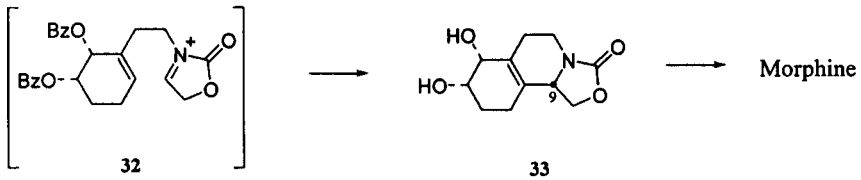


Figure 9. Octahydro Isoquinoline Synthesis.

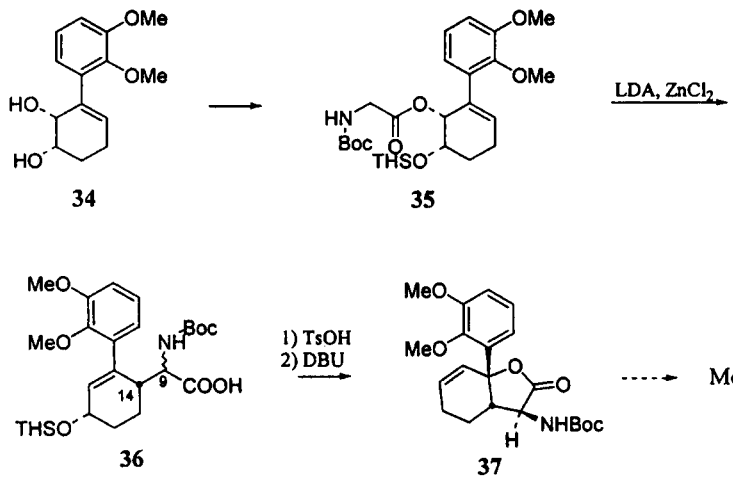
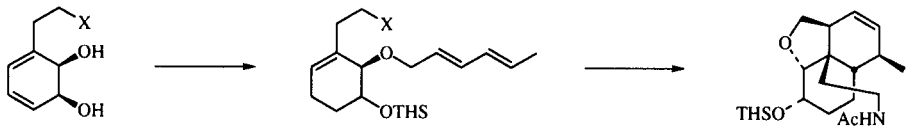


Figure 10. Claisen Rearrangement Approach to Morphine; THS: Dimethylthexylsilyldimethyl(1,1,2-trimethylpropyl)silyl; DBU: 1,8-Diazabicyclo-[5.4.0]undec-7-ene.



X = Br, N_3, NHAc
38

X = NHAc
39

40

Figure 11. Intramolecular Diels-Alder Cycloaddition Approach to Morphine.

3. Summary.

The use of the homochiral synthons available *via* biocatalysis leads to an efficient design for structurally related alkaloids. The multi-generation effort is crucial to the successful and practical syntheses of the title compounds. Without the return to accomplished syntheses and improvements in any troublesome parts thereof, no progress can be expected. The combination of proper technologies, creative design, and the use of enzymes for introduction of chirality results in brevity and efficiency and ultimately provides the target compounds in an environmentally benign fashion.

Acknowledgements.

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