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Total Synthesis of (+)-Cassaine Utilizing an Anionic Polycyclization Strategy

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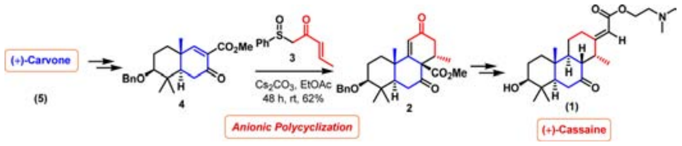
ABSTRACT



A stereoselective total synthesis of (+)-cassaine (1) via an anionic polycyclization methodology is described. Commercially available (+)-carvone (5), the only chiral source, was used to fix the entire stereochemistry of the natural product. Anionic polycyclization of a new substituted 2-(methoxycarbonyl)cyclohex-2-en-1-one (4) with known 1-phenylsulfinyl-3-penten-2-one (3) provided the versatile tricycle (2) with requisite stereochemistry. A sequence of functional group manipulations of tricycle (2) furnished the natural product 1.

In 1988, we reported a base catalyzed stereocontrolled synthesis of *cis*-decalins,[1] from a substituted Nazarov reagent[2] (γ,δ-unsaturated-β-ketoester) and 2-carbomethoxy-2-cyclohexenone, which is now well recognized as an anionic polycyclization. This reaction comprises two consecutive Michael additions and is analogous to the Diels–Alder cycloaddition.[3] Subsequently we disclosed the synthesis of a racemic 13-α-methyl 14-α-hydroxy steroid,[4] a novel synthesis of functionalized optically active 13-β-methyl 14-β-hydroxy steroid,[5] and a convergent synthetic approach to a tetracyclic steroid nucleus using several bicyclic Nazarov reagents.[6] This anionic polycyclization strategy proved once again its versatility in the first stereoselective total synthesis of the complex cardioactive steroidal natural product ouabain.[7]

Most recently, Brückner and Petrovic reported the synthesis of densely functionalized octalindiones from acceptor-substituted benzoquinone monoketals and various substituted Nazarov reagents using anionic polycyclization.[8] We have also reported a versatile synthetic strategy involving anionic polycyclization to access various tricycles related to quassinoids and terpenoids from suitably substituted 2-(formyl)cyclohex-2-en-1-one and 2-(nitrile)-cyclohex-2-en-1-one with diverse Nazarov reagents.[9] Herein we report a stereoselective total synthesis of (+)-cassaine (**1**) using this strategy.

The *Erythrophleum* alkaloid (+)-cassaine (**1**), a nonsteroidal inhibitor of Na^+-K^+-ATPase, was isolated by the Dalma group in 1935,[10] from the bark of *Erythrophleum guinneese*. Structurally, **1** is a *N*,*N*-dimethylaminoethyl ester of monocarboxylic acid of the diterpenoid. Turner and co-workers reported the structural elucidation of **1**,[11] and the same group disclosed the first relay total synthesis.[12] It is a specific inhibitor of monovalent cation

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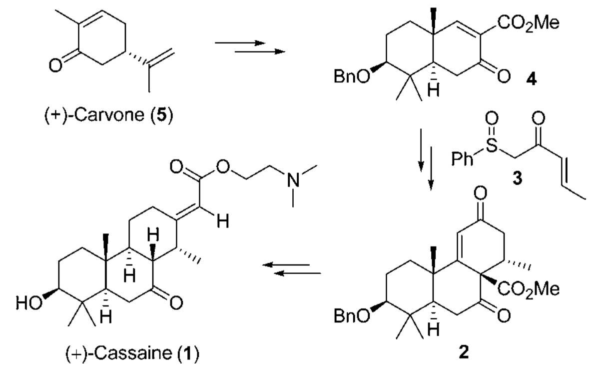
Scheme 1. Synthetic Analysis of (+)-Cassaine (**1**)



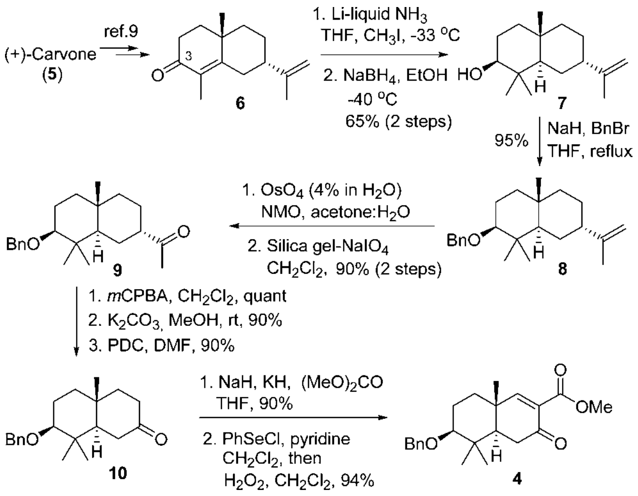
transport and of the Na$^+$-K$^+$-ATPase, and known to possess remarkable pharmacological action similar to that of the digitalis glycosides such as digitoxin, even though the chemical structures are quite different.[13] Impressed by the interesting biological profile of **1**, we previously reported the stereoselective total synthesis using our own protocol of the transannular Diels–Alder reaction.[14]

In our continuing quest for new applications of anionic polycyclization reactions, and in combination with the very interesting cardiotonic properties of (+)-cassaine, we examined the efficacy of this reaction in a stereocontrolled total synthesis of (+)-cassaine.

Our synthetic strategy is illustrated in Scheme 1, which was based on the initial construction of suitably functionalized tricycle **2**, which contains, in principle, all the functionalities required for the construction of natural product **1**. Tricycle **2** would be readily prepared from the new substituted 2-(methoxycarbonyl)cyclohex-2-en-1-one **4** and 1-phenylsulfinyl-3-penten-2-one (**3**) using Cs_2CO_3 mediated anionic polycyclization reaction. β-Keto ester **4** could be readily prepared from (+)-carvone (**5**) using our previously reported analogous synthetic route.[9]

The preliminary steps in the synthesis of the β-keto ester **4** drawn from our previous studies on the synthesis of analogous *trans*-decalins were successful.[9] Thus, the synthesis of **4** started with enone **6** (obtained by the Birch reduction followed by Robinson annulation of (+)-carvone (**5**) and ethyl vinyl ketone),[9,15] which was subjected to reductive methylation (Li, liquid NH_3, CH_3I) followed by highly stereocontrolled reduction of the C3 ketone functionality (steroid numbering) with $NaBH_4$ providing the β-alcohol **7**.[16] Benzyl protection of alcohol **7** using standard reaction conditions afforded the benzylether **8** in 95% yield. Having served its diastereomeric control purpose in the annulation reaction, the isopropenyl group of **8** was subjected to OsO_4 mediated dihydroxylation, followed by silica gel supported-$NaIO_4$[17] cleavage to give ketone **9** (Scheme 2).

Scheme 2. Synthesis of β-Keto Ester **4**



Baeyer–Villiger oxidation of ketone **9**, followed by saponification and PDC oxidation, afforded the ketone **10**. Carbomethoxylation[18] of ketone **10**, and subsequent phenylselenation and dehydroselenation, gave the desired substituted 2-(methoxycarbonyl)cyclohex-2-en-1-one **4**,[19] which was used as a key fragment in the anionic polycyclization reaction (Scheme 2).

Anionic polycyclization of the new substituted 2-(carbomethoxy)-α,β-unsaturated ketone **4** and known[9] 1-phenyl-sulfinyl-3-pent-2-one (**3**) with cesium carbonate in EtOAc at room temperature furnished the diastereomerically pure tricycle **2** in 62% yield, possessing the desired *axially* oriented C14 methyl group, which is very difficult to obtain by other methods.[14] The stereochemistry of the tricycle **2** was assigned based on comparison of the spectral data with our recently reported analogous tricycles.[9] As we observed in our earlier studies, the stereochemical outcome at C8 and C14 of **2** is directly influenced by the C10 angular methyl group of **4**, which forces the Nazarov reagent **3** to enter from the α-face in an *endo* approach.[9,20] Base (NaOEt in EtOH) induced decarbomethoxylation of **2** with concomitant olefin migration afforded enone intermediate **11** in 90% yield (Scheme 3).

Selective reduction of the C12 ketone functionality of **11** with $NaBH_4$ at −78 °C provided the C12 α-alcohol **12**, which was protected as its TBS ether **13** in 96% yield. Palladium (Pd/C, 15 psi of H_2, 24 h) catalyzed selective hydrogenation of benzyl ether **13** gave the alcohol **14** in 90% yield, without affecting the enone functionality (Scheme 3).

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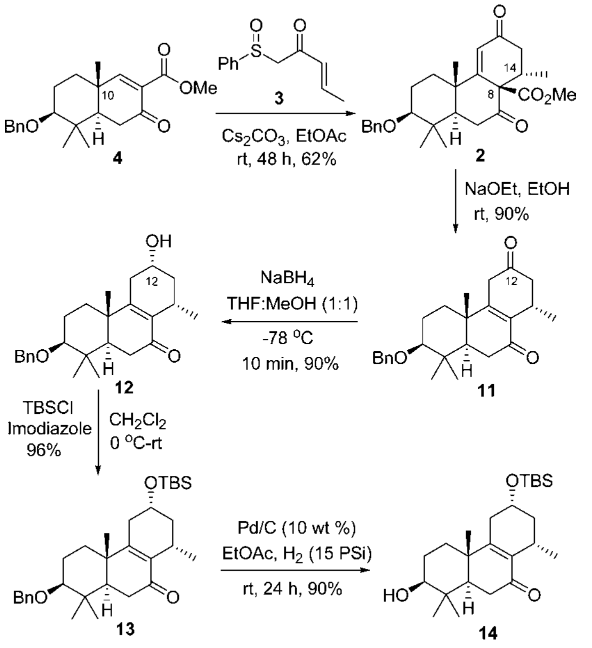
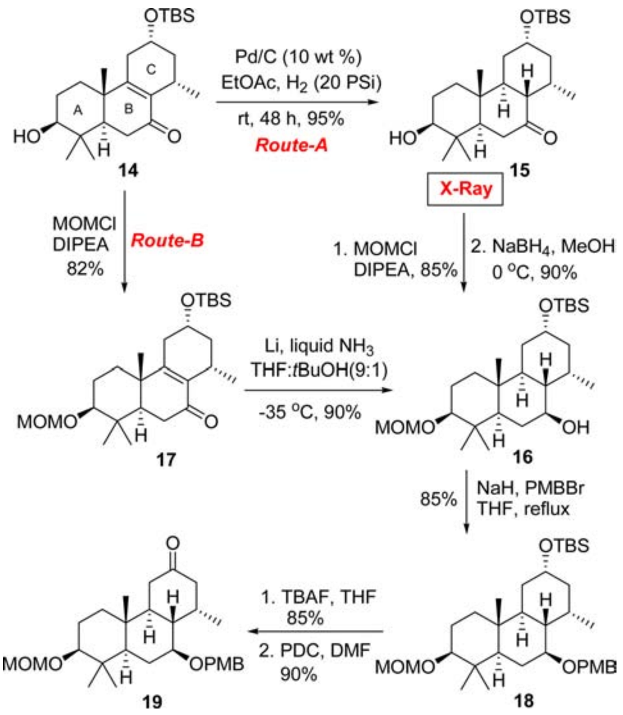
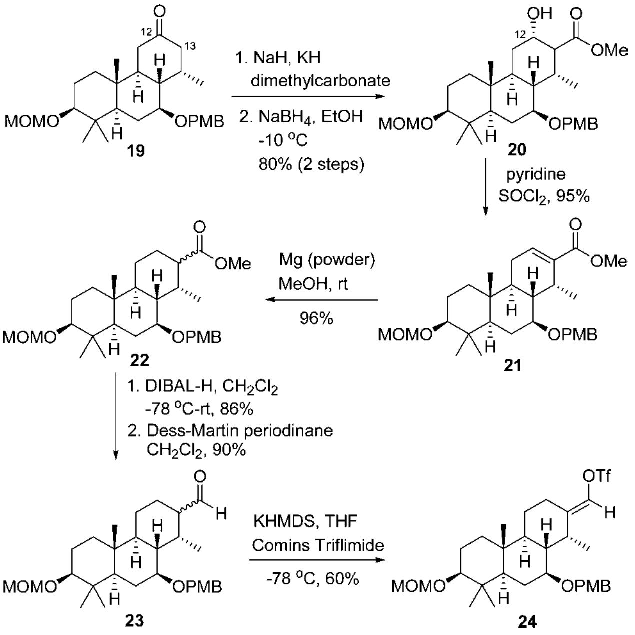
Scheme 3. Synthesis of Tricycle **14**



Scheme 4. Synthesis of Ketone Intermediate **19**



Scheme 5. Synthesis of Vinyl Triflate **24**



Our next aim was to convert tricycle **14** into ketone **19** via *trans-antitrans* (TAT) tricycle **16** having the desired stereochemistry of (+)-cassaine (**1**). Pd/C catalyzed hydrogenation (H$_2$, 20 psi, 48 h) of enone **14** furnished ketone **15** (Route A). To our delight, we obtained only the desired ketone **15** with the B/C *trans* ring junction, which might be due to the stepwise reduction of the enone double bond, via steric hindrance promoted inversion at C8 (or) initial reduction to give B/C *cis* ring junction followed by Pd/C facilitated epimerization at the active C8 position. The structure of the tricycle **15** was rigorously confirmed by single crystal X-ray diffraction analysis.[21] MOM Protection of alcohol **15** followed by stereoselective NaBH$_4$ reduction gave the alcohol **16** in 90% yield. Alcohol **16** can also be prepared from enone **14** in an alternative route (Route B), in which conversion of **14** into its MOM ether **17** followed by highly stereoselective Birch reduction (Li, liquid NH$_3$, *t*BuOH-THF) of the enone functionality of **17** furnished the alcohol **16** in 90% yield (Scheme 4).[22]

PMB protection of alcohol **16** using standard reaction conditions gave the PMB ether **18** in 85% yield. Deprotection of TBS ether **18** with TBAF in THF gave the corresponding alcohol, which was oxidized to ketone **19** with PDC in anhydrous DMF (Scheme 4).

After successful synthesis of ketone **19** having *trans-antitrans* (TAT) stereochemistry, we turned our attention toward a crucial manipulation, introduction of the C13 exocyclic olefinic functionality by taking advantage of the C12 ketone functional group. Carbomethoxylation[17] of ketone **19** followed by chemoselective reduction of the β-keto ester using NaBH$_4$ furnished the β-hydroxy ester **20** in 80% yield (two steps), which was treated with SOCl$_2$ in pyridine to afford the α,β-unsaturated ester **21**.[23] Magnesium in the methanol reduction of α,β-unsaturated ester **21** furnished the corresponding saturated ester **22** (as a diastereomeric mixture at C13) in 96% yield.[24]

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[21] See the Supporting Information for crystallographic data.

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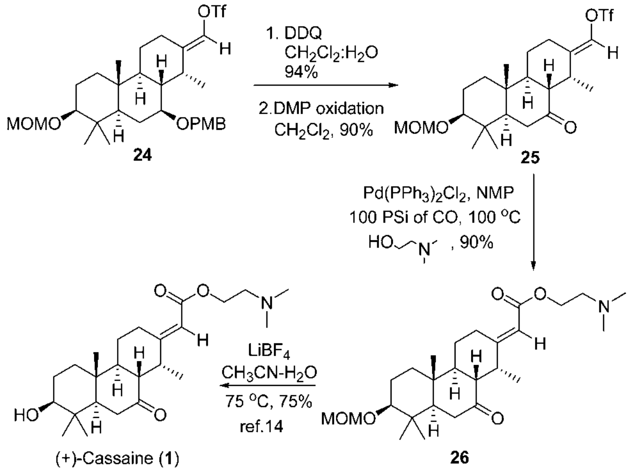
Scheme 6. Synthesis of (+)-Cassaine (**1**)



DIBALH reduction of ester **22** gave the alcohol, and subsequent oxidation with Dess-Martin periodinane provided the aldehyde **23**. After several experiments, it was realized that aldehyde **23** could be converted into the *E*-vinyl triflate **24** with KHMDS and Comins reagent (*N*-(5-chloro-2-pyridyl)triflimide) (Scheme 5).[25]

Completion of the synthesis of (+)-cassaine (**1**) is described in Scheme 6. PMB deprotection followed by Dess-Martin periodinane oxidation of **24** gave the ketone **25**. Pd(II) catalyzed carboalkoxylation of vinyl triflate **25** using K_2CO_3, *N*,*N*-dimethylamino ethanol, carbon monoxide (100 psi), and 1-methyl-2-pyrrolidinone (NMP) furnished the known OMOM-cassaine **26**.[14] Ultimately, deprotection of the MOM ether was accomplished with $LiBF_4$ in aqueous acetonitrile to give (+)-cassaine (**1**) in 75% yield. The spectroscopic data of OMOM-cassaine **26** and (+)-cassaine (**1**) were in full accordance with those reported in the literature in all respects.[14,26]

In conclusion, an efficient stereocontrolled total synthesis of (+)-cassaine (**1**) has been achieved via a Cs_2CO_3 mediated anionic polycyclization strategy. (+)-Carvone (**5**) was used as the only chiral source to fix the entire stereochemistry of the natural product. Further developments on this anionic polycyclization approach and studies toward the synthesis of quassinoids (bruceantin and quassin) are now being pursued in our laboratory and will be reported in due course.

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Supporting Information Available. Experimental details, physical and NMR spectral data for all new compounds; X-ray crystallographic data for **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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