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Total Synthesis of (+)-Cassaine via Transannular Diels−Alder Reaction

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Abstract: A full account of the total synthesis of (+)-cassaine (**1**) using the transannular Diels−Alder (TADA) reaction as the pivotal construction is described. The strategy began from Evans' oxazolidine **8**, the only chiral source used for the total stereochemical outcome of the target molecule. The key intermediate **3** was obtained from **8** in 10 steps in 40% overall yield. Following extensive optimization, the coupling of **3** on both ends with another densely functional partner **2** followed by TADA reaction on macrocycle **4** cleanly furnished the tricycle **5**. The stereochemical outcome in **5** was expected via a least-energetic transition state **T4**. A stereoselective reduction, hydroboration, and methyl cuprate 1,4-addition along with a few other functional interconversions transformed **5** into the key intermediate **37**. Final tethering of dimethylaminoethyloxycarbonyl along with epimerization at C8 and alcohol deprotection at C3 yielded the natural product **1**.

Introduction

Our laboratory has for many years investigated the synthetic potential of the transannular Diels−Alder (TADA) reaction for the construction of polycyclic natural and non-natural products.[1] We[2] and others[3] have successfully used this reaction as a key step in the total synthesis of natural products. We now report the successful construction of (+)-cassaine (**1**) using this strategy.

(+)-Cassaine is a nonsteroidal inhibitor of Na^+,K^+-ATPase that is known to possess a pharmacological action similar to that of the digitalis glycosides, such as digitoxin, even though their structures are quite different.[4] In 1935, the Dalma group[5] isolated (+)-cassaine from the bark of *Erythrophleum guinneese*. The structural elucidation was achieved by the Turner group[6] in 1959. In 1967, the same group realized the only total synthesis of (+)-cassaine, although they had some difficulty with the functionalization of rings B and C, and at the same time they established its absolute configuration.[7] (+)-Cassaine has been the subject of work in the biological area because of its efficient cardiotonic property, equal to that of digitalis glycoside.

Structurally, **1** features a trans−anti−trans (TAT) tricyclic system possessing six stereocenters and an *exo*-α,β-unsaturated ester containing a dimethylamino group (Figure 1). Our strategy for the synthesis of **1** was based on the expected stereocontrolled construction of trans−anti−cis (TAC) tricycle **5** through the use of the TADA reaction on trans−trans−trans (TTT) macrocyclic triene **4** (Figure 1).[1e] Macrocycle **4** was available from **2** and **3**, as shown in our previous studies.[8] Steric bias in **5** was predicted to be useful for reducing the keto group at C3 stereoselectively and introducing an α-hydroxyl group at C7. Also, elimination of the C14 alkoxy group in ring C would produce a TAC tricycle whose structural feature would allow the introduction of the axially oriented C14 methyl group having the desired α configuration. Moreover, when this 1,4-addition reaction was carried out on a tricycle containing a conjugated aldehyde, such as **6**, the enolate formed during the reaction pathway could be trapped to give the *exo*-triflate **7**, which should serve as a basis for tethering of the remaining amino ester tail.

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(7) The synthesis was realized by first producing a racemic advanced tricyclic intermediate that was found to be identical with the same compound obtained by degradation of (+)-cassaine. The degraded material was used as a relay compound to complete the synthesis. See: Turner, R. B.; Buchardt, O.; Herzoy, E.; Morin, R. B.; Riebel, A.; Sanders, J. M. *J. Am. Chem. Soc.* **1966**, *88*, 1766.

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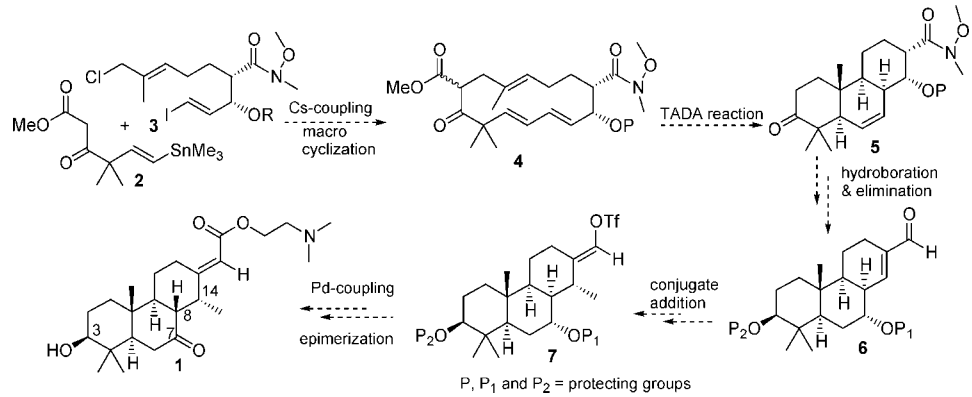
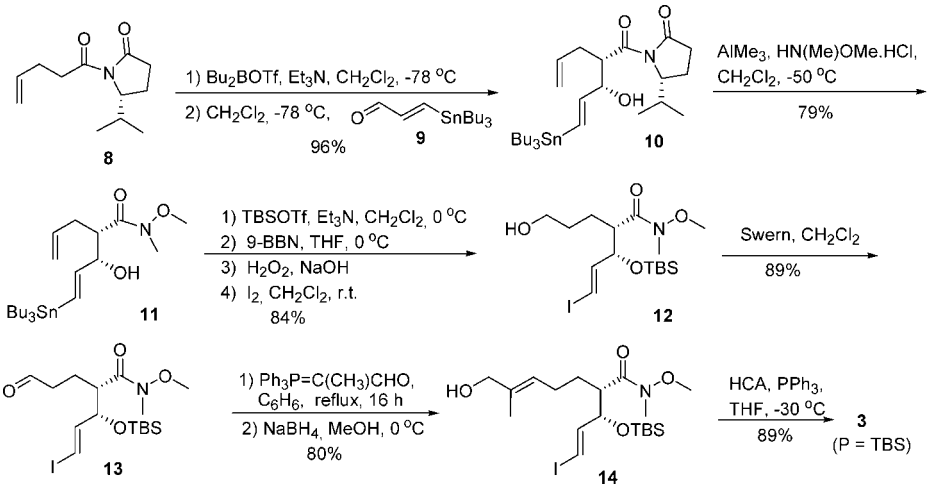


Figure 1. Synthetic analysis of **1**.

Scheme 1. Synthesis of Intermediate **3**



Finally, carbonylation followed by oxidation at C_7 would allow the required epimerization at C8 to furnish the TAT framework, yielding **1**.

Results and Discussion

In order to increase the yield efficiency for the synthesis of the previously reported macrocycle **4**, a novel route was elaborated for the eastern part **3** (Scheme 1). The synthesis began with an Evans aldol condensation[9] between known imide **8** and aldehyde **9** in excellent yield. Transformation of **10** to Weinreb amide[10] **11** followed by protection of the alcohol as the TBS ether, regioselective oxidation of the terminal olefin to a primary alcohol using 9-BBN/H_2O_2,[11] and exchange of stannane with iodide realized vinyl iodide **12** in 72% yield from **8**. The primary alcohol was oxidized using the Swern protocol[12] to give aldehyde **13** in 89% yield. A Wittig reaction was performed on aldehyde **13** using triphenylphosphoranylidene propionaldehyde[13] to give the α,β-unsaturated aldehyde having only the E geometry, and after a reduction with sodium borohydride, allylic alcohol **14** was obtained in 80% yield. Transformation of that alcohol to the chloride **3** was carried out using the Magid procedure[14] in 89% yield. In summary, the eastern part of the macrocycle was synthesized in 10 steps in 40% overall yield, which was much better than the 12% yield obtained in our previous synthesis.

Coupling of chloride **3** with the known stannane **2**[2e] was achieved in the presence of cesium carbonate, cesium iodide, and crown ether 18-crown-6 in acetone in an excellent yield of 95% (Scheme 2). When the reaction was performed in the absence of the crown ether, the yield dropped to 60%. This result suggests that the crown ether can complex the cesium, facilitating the coupling reaction. Once the desired precursor **15** had been formed, the macrocyclization was achieved using conditions developed in our laboratory to give a diastereomeric mixture of macrocycles **4** in 71% yield.[15] This result is excellent in view of the fact that 14-membered TTT macrocycles are in general strained and usually difficult to obtain in high yields.[1e]

To avoid the diastereomeric mixture of macrocycles, a macrocyclization/decarboxylation reaction was planned. Allyl

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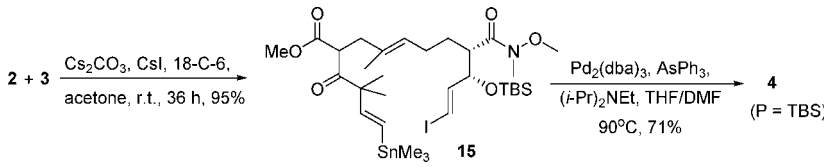
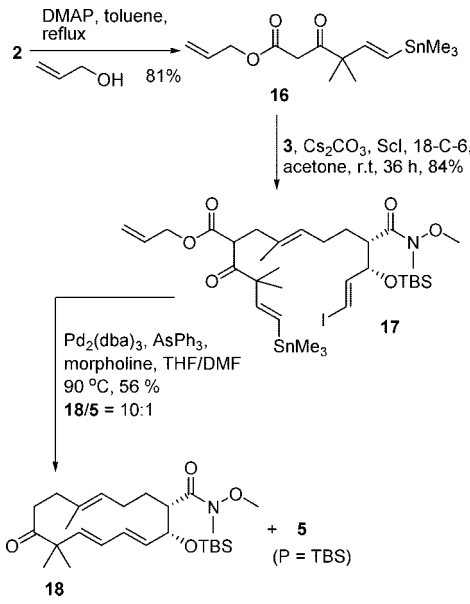
(15) Marsault, E.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 3317.

Scheme 2. Synthesis of Macrocycle **4**



Scheme 3. Synthesis of Intermediates **18** and **5**



ester can be easily decarboxylated in the presence of palladium. Thus, stannane **2** was transformed into the corresponding stannane allyl ester **16** in 81% yield using Taber's protocol[16] (Scheme 3). This β-keto ester was coupled to chloride **3** in the same manner as previously described[8] to give **17** in 84% yield. The macrocyclization/decarboxylation[17] was effected in the presence of tris(dibenzylideneacetone)palladium, triphenylarsine, and morpholine at 90 °C to give a mixture of macrocycle **18** and tricycle **5** in 56% yield and a 10:1 ratio.

Once macrocycles **4** and **18** were in hand, the TADA reaction was carried out at a higher temperature of 123 °C, since it is known that some tricycle can be observed at 90 °C during macrocyclization of **17**. As indicated in Scheme 4, **4** gave a mixture of the TAC tricycle **19** along with its decarboxylated TAC derivative **5**. Heating of **19** at 150 °C produced TAC tricycle **5** in high yield. On the other hand, heating the decarboxylated macrocycle **18** at 123 °C produced only the TAC tricycle **5**, as expected.

In order to verify whether the synthesis could be shortened, a new macrocycle in which the C14 alkoxy group was replaced by methyl group was designed. Indeed, with the alkoxy group replaced by a methyl group, the new macrocyle could give a much more straightforward synthesis of **1** because the C14 methyl group would have the right stereochemistry after the TADA reaction, provided that this process is still stereoselective (Figure 2).

The synthesis of the new macrocycle began with a crotyl boration using the Roush reagent **20** on the aldehyde **21** to give alcohol **22** in 47% yield (74% based on recovered starting material) (Scheme 5).[18] The secondary alcohol was then protected as a TBPDS ether in 95% yield, and the double bond was ozonolyzed to obtain the desired aldehyde **24** in 80% yield. A Takai reaction[19] was performed on **24** using chromium chloride and iodoform to give the (*E*)-iodoalkene, and deprotection of the TBS ether was achieved to give the primary alcohol **25** in 73% yield for the two steps. This alcohol was oxidized with Dess−Martin periodinane to yield aldehyde **26** in 90% yield. The same sequence of a Wittig reaction followed by sodium borohydride reduction was used as before to form the alcohol **27** in 71% yield. This alcohol was then transformed into the corresponding allylic chloride **28** via the Magid procedure in 90% yield.

Coupling of chloride **28** and the known stannane **2** using the same conditions as described earlier afforded triene **29** in a good yield of 75% (Scheme 6). The macrocyclization to give **30** was then realized in 74% yield using Stille coupling conditions.

The TADA reaction of macrocycle **30** was carried out in toluene in a sealed tube at 115 °C, but unfortunately, the reaction was not stereoselective and yielded many products that were not separable by chromatography. GC−MS and NMR analyses of that mixture clearly indicated the presence of four decarboxylated products with the same mass (equal to that of the target tricycle), thereby revealing that the TADA reaction with macrocycle **30** was not stereoselective.

The two macrocycles **4** and **30**, which differ only in the two substituents at C13 and C14, gave totally different results for their TADA reactions. It was known from our previous model studies[1e] that a TTT macrocycle can lead to two tricyclic structures, TAC and CAT. However, the TADA reaction can favor one diastereoisomer over the other if the steric and/or stereoelectronic factors are well set in favor of a given macrocycle. This was the case for **4**, reaction of which led only

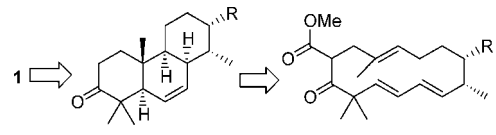
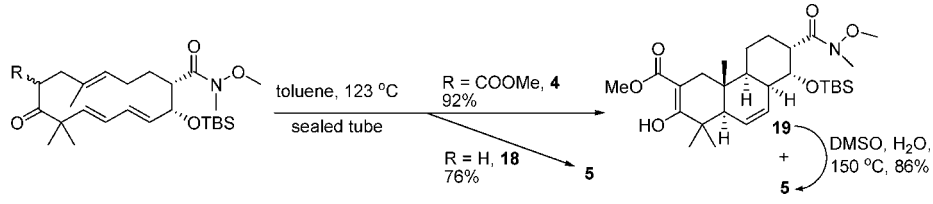
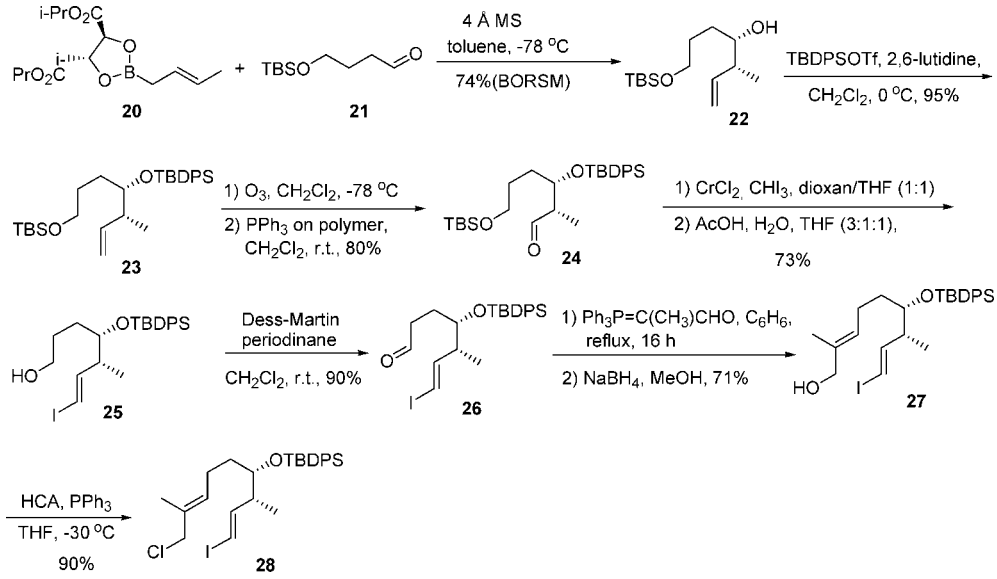


Figure 2. New synthetic analysis of **1**.

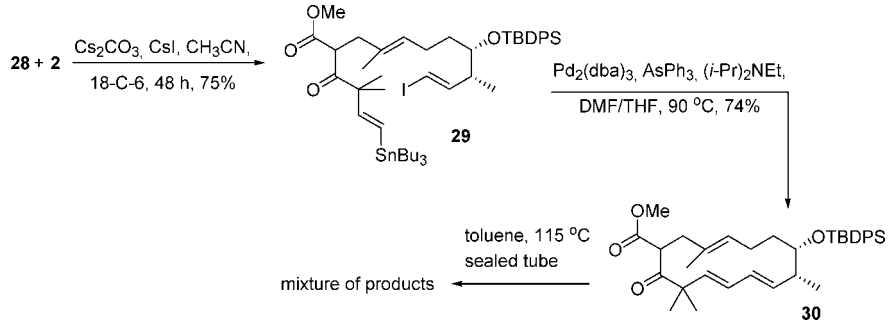
Scheme 4



Scheme 5



Scheme 6. Synthesis and TADA Reaction of Macrocycle **30**



to tricycle **5**. The specific formation of that tricycle can be explained by examining the four possible transition states having a boat−boat−chair conformation (Figure 3); because of the *gem*-dimethyl unit at C4, the usually preferred chair−boat−chair conformation is eliminated due to severe steric repulsion. The transition state $\mathbf{T_1}$, which leads to CAT tricycle $\mathbf{X_1}$, suffers from severe steric interactions of the diene with the alkoxy group on one side and one of the methyl groups of the *gem*-dimethyl unit on the other side. In case of transition state $\mathbf{T_2}$, which leads to CAT tricycle $\mathbf{X_2}$, a steric repulsion exists between the diene and the *gem*-dimethyl unit. In addition, there is a stereoelectronic effect caused by the alkoxy group at C14, which is antiperiplanar to the new C−C bond formed during the Diels−Alder reaction.[20] The resulting inductive effect of the C−OR bond, which withdraws electrons from the C−C bond being formed, increases the energy of this transition state as previously observed and is thus also disfavored.

On the other hand, advancement along the transition states $\mathbf{T_3}$ and $\mathbf{T_4}$ can both lead to TAC tricycles ($\mathbf{X_3}$ and $\mathbf{X_4}$, respectively). While $\mathbf{T_4}$ experiences no noticeable steric repul-

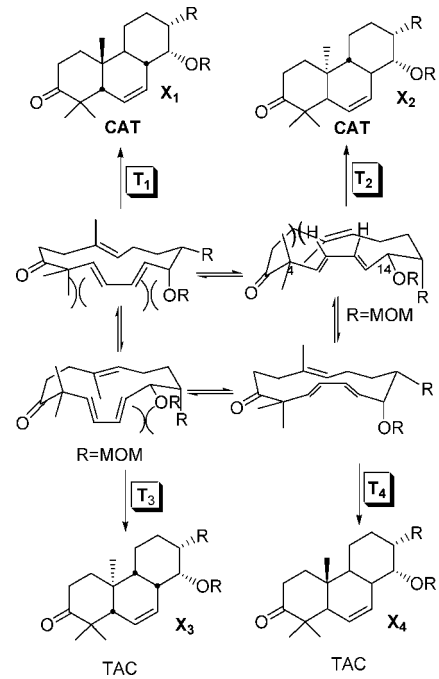


Figure 3. Possible transition states for the cyclization reaction.

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(17) (a) Krapcho, A. P.; Glynn, G. A.; Grenon, B. J. *Tetrahedron Lett.* **1967**, *8*, 215. (b) Krapcho, A. P. *Synthesis* **1982**, *805*, 893.
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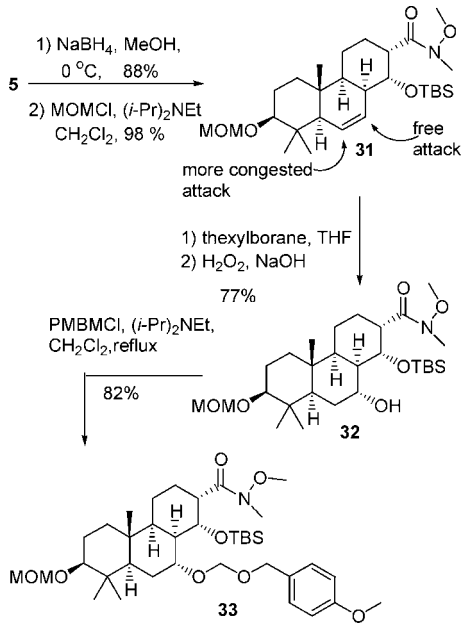
Scheme 7. Synthesis of Intermediate **33**



sion, there is an important steric interaction that prevails between the pseudoaxial R group and the diene in $\mathbf{T_3}$. In addition, $\mathbf{T_4}$ is also favored because of a destabilizing stereoelectronic effect in $\mathbf{T_3}$ similar to that in the case of $\mathbf{T_2}$. As a consequence, the only favored product during the TADA reaction is the TAC tricycle $\mathbf{X_4}$ that evolves from the most favored transition state $\mathbf{T_4}$. Thus, it is interesting to point out that the alkoxy group at C_{14} plays a major role in this TADA reaction. Since the macrocyclic precursor contains two stereocenters and is chiral, the transannular strategy allows complete stereochemical control, yielding a single chiral tricycle containing four new stereocenters in a TAC arrangement (i.e., **5**) in a single step under mild conditions. In addition, it is interesting to point out that the transannular strategy allows the use of a nonactivated dienophile.

In the case of macrocycle **30**, where the alkoxy group is replaced by a methyl group, the destabilizing stereoelectronic effect that eliminates $\mathbf{T_2}$ and $\mathbf{T_3}$ does not exist. On the other hand, when the various steric effects are examined, it appears that transition state $\mathbf{T_4}$ cannot be considered to have an energy low enough to completely eliminate $\mathbf{T_2}$ and $\mathbf{T_3}$. Thus a mixture of stereoisomers is formed.

The synthesis was therefore continued with tricycle **5**. Because of the steric hindrance caused by the C4 β-methyl and

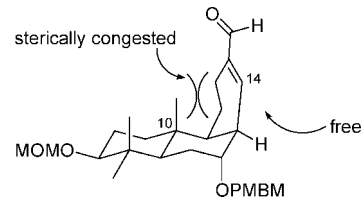


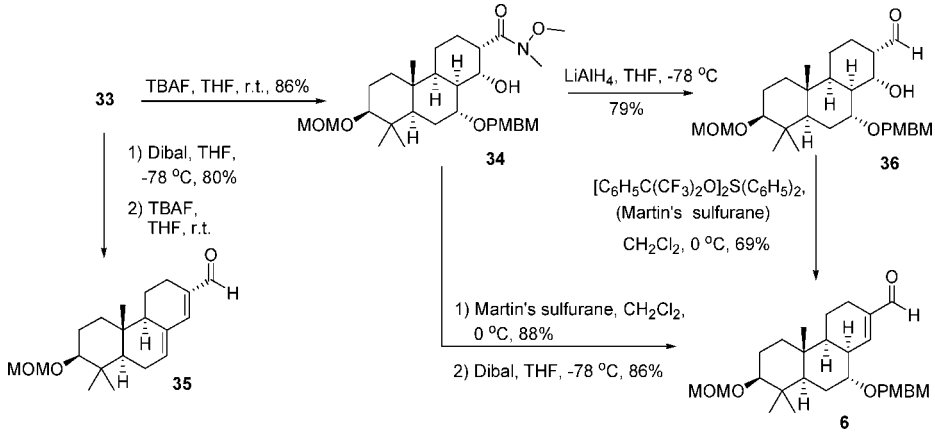
Figure 4. Feasibility of nucleophilic attack.

C10 methyl groups, the ketone at C3 was stereoselectively reduced with sodium borohydride and the resulting β alcohol (88% yield) protected as a MOM ether in 98% yield (Scheme 7). Having thus constructed the basic skeleton of the molecule in the form of **31**, we turned our attention to the introduction of a hydroxyl group at C7 by hydroboration of the double bond formed during the TADA reaction. We expected that the regioselectivity of the reaction would be controlled by the steric bias generated by the *gem*-dimethyl group and the C10 methyl group and hence that the borane addition would favor the α side at C_7.

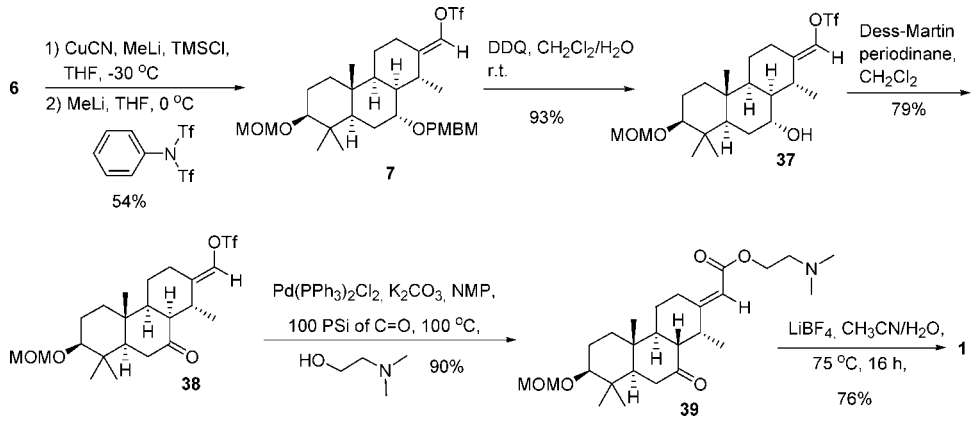
The reaction was first attempted with a borane−THF complex, but this approach yielded a mixture of three alcohols. We were even not rewarded when the reaction was carried out with larger borane sources, such as 9-BBN and disiamylborane, where only the starting material was recovered. Elevated temperatures also proved unfruitful. The reaction was then tried with thexylborane, which is intermediate in size, and to our delight, we obtained only the desired α alcohol **32** in 77% yield. The newly formed alcohol was then protected with *p*-methoxybenzyloxymethyl chloride to get **33** in 82% yield.

As we had by this point set the rings A and B conveniently for the final operations, we turned our attention to a crucial manipulation, namely, introduction of an α-methyl group in the place of the existing hydroxyl group in ring C. Compound **33** was deprotected with TBAF to give **34** in 86% yield (Scheme 8). DIBAL-H reduction of the Weinreb amide was surprisingly unsuccessful and led to decomposition. Inversion of the sequence was then attempted. DIBAL-H-mediated reduction of **33** worked well to give the corresponding aldehyde in 80% yield, but the deprotection step led to the undesired elimination product **35**. However, reduction of the Weinreb amide was successfully achieved with $LiAlH_4$ at −78 °C to give aldehyde **36** in 79% yield.[21] Several sets of elimination conditions for forming the enal were then tested, and Martin's sulfurane[22] was found to be a suitable reagent for transforming **36** to desired enal **6** in 69% yield. Here again, the inversion of the sequence was

Scheme 8. Synthesis of Intermediate **6**



Scheme 9. Completion of the Synthesis of **1**



investigated, and we were delighted to see better results. Accordingly, elimination of alcohol **34** with Martin's sulfurane at 0 °C in dichloromethane worked well (88% yield) to give the unsaturated amide, which on reduction with DIBAL-H furnished the desired enal **6** in 86% yield.

Examination of the TAC shape of enal **6** (Figure 4) indicated that essentially only the α-face was sterically available for the 1,4-addition of a methyl group, leading to the desired α stereochemistry at C14. After severe experimentation on models, the addition was realized using copper cyanide, methyllithium, and TMSCl at −30 °C and led to the desired (although unstable) enol ether (Scheme 9).[23] To avoid decomposition, this enol ether was immediately transformed into the corresponding stable triflic enol ether **7** using methyllithium and *N*-phenyltrifluoromethane sulfonimide[24] in THF in 54% yield for the last two steps.

The successful introduction of the methyl group at C14 and the simultaneous formation of the triflic enol ether made completion of the synthesis possible at last. Deprotection of *p*-methoxybenzyloxymethyl-protected hydroxyl group was achieved using DDQ to give the corresponding alcohol **37** in 93% yield, and subsequent oxidation was accomplished with Dess−Martin periodinane to form ketone **38** in 79% yield. An X-ray diffraction crystal structure analysis provided absolute proof of the structure of **38** (Figure 5).

The next crucial task was the tethering of the dimethylaminoethyl ester group along with epimerization. We assumed that the preceding coupling conditions would also facilitate the epimerization at C8. Pleasingly, the coupling was realized using dichlorobis(triphenylphosphine)palladium, potassium carbonate, and *N*,*N*-dimethylaminoethanol in *N*-methylpyrrolidinone,[25] giving **39** with the desired epimerization to give the TAT stereochemistry in 90% yield. Finally, deprotection of the MOM ether was carried out with lithium tetrafluoroborate in a mixture of acetonitrile and water to yield (+)-cassaine **1** in 76% yield. Since very little supporting data for (+)-cassaine **1** was available in the literature for comparison, we sought a thorough analysis to prove the epimerization under the coupling conditions. With the help of COSY, we could clearly position H12, H3, H14, $H6_{ax}$, $H6_{eq}$, H8, and H5 along with a few other protons,[26] all of which were in good accordance with previous analyses of analogous compounds.[27] H14 couples with H8 with a small coupling constant ($J = 3.57$ Hz), whereas H8 couples with H9 with large coupling constant ($J = 12.62$ Hz),[27] which is possible only after epimerization of proton H8 to the axial position. In addition, NOESY (Figure 6) revealed that H8 is spatially closer to H14, $H6_{ax}$, and the CH_3 group on C10, whereas H14 is closer to the olefinic hydrogen, providing further support for the inversion.[27b]

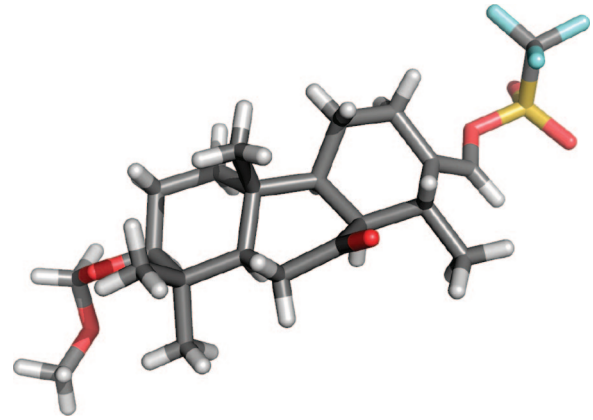


Figure 5. X-ray structure of compound **38** (ORTEP view).

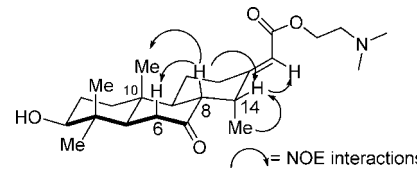


Figure 6. NOE interactions in compound **1**.

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Conclusion

In summary, macrocycle **4**, which was obtained in two steps from building blocks **2** and **3**, was converted into (+)-cassaine **1** in 13 steps using the following key transformations: (1) a completely selective transannular Diels−Alder reaction with a nonactivated dienophile, leading to a chiral TAC tricycle having four new stereogenic centers; (2) a regioselective hydroboration to introduce an alcohol at C7; (3) a stereocontrolled 1,4-addition on the TAC tricyclic framework. leading to the α-oriented methyl group at C14 and the regioselective formation of an enol triflate; and (4) a successful carbonylation with a concomitant epimerization at C8 to produce **1**.

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Supporting Information Available: Full experimental details, ^{1}H and ^{13}C NMR spectra, full characterization of all of the new compounds described herein, and a CIF file for compound **38**. This material is available free of charge via the Internet at http://pubs.acs.org.

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