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Progress toward the Total Synthesis of Cassaine via the Transannular Diels–Alder Strategy

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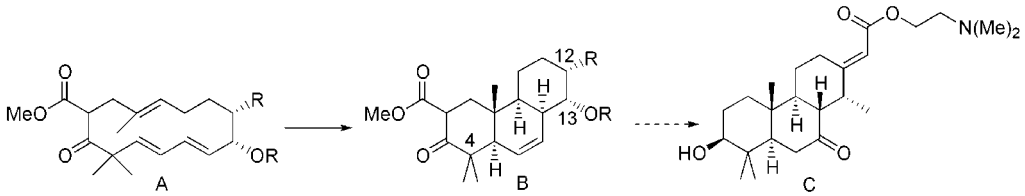
ABSTRACT



The transannular Diels–Alder reaction of *trans-trans-trans* macrocyclic triene A, bearing two *cis* substiuents in C_{12} and C_{13} as well as a *gem*-dimethyl in C_4, was studied. Under thermal conditions, only the desired *trans-anti-cis* tricycle B was obtained. This tricycle represents an advanced intermediate toward the total synthesis of cassaine C.

In the past years, studies on the transannular Diels−Alder (TADA) reaction have proven this strategy to be a powerful tool for the stereocontrolled synthesis of polycyclic compounds.[1,2] The *trans-trans-trans* (TTT) trienes turned out to be the most difficult ones to macrocyclize;[3] on the other hand, their TADA reactions proved to be the easiest ones to perform. Hence the TTT series has an interesting synthetic potential.

The TTT system can in principle lead to two adducts, namely, the *trans-anti-cis* (TAC) and the *cis-anti-trans* (CAT) tricycles.[1,3] We have previously demonstrated that 14-membered TTT macrocyclic triene **1** with *cis* substituents led to the specific formation of TAC tricycle **2** due to steric hindrance from the malonate and the alkoxy group (Figure 1).[4] This result was very interesting since only one of the four possible products was obtained (two TAC and two CAT), having the desired stereochemistry of a number of natural products. However, from a synthetic point of view, the malonate connector was an obstacle to further elaboration of ring A.

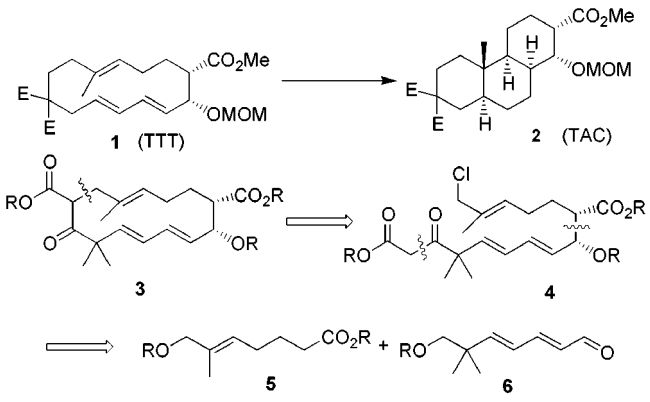


Figure 1.

(1) Deslongchamps, P. *Pure Appl. Chem.* **1992**, *64*, 1831.
(2) For applications in total synthesis, see: (a) Toró, A.; Nowak, P.; Deslongchamps, P. *J. Am. Chem. Soc.* **2000**, *122*, 4526. (b) Bélanger, G.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 285. (c) Germain, J.; Deslongchamps, P. *Tetrahedron Lett.* **1999**, *40*, 4051.
(3) Lamothe, S.; Ndibwami, A.; Deslongchamps, P. *Tetrahedron Lett.* **1988**, *29*, 1639, 1641.
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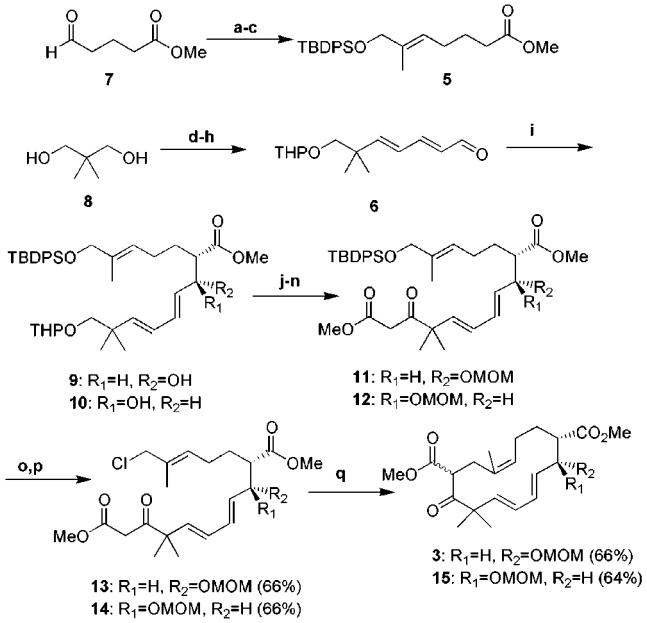
We wish now to report the synthesis of 14-membered TTT macrocycle **3** with *cis* substituents in pro-ring C, where the malonate connector was replaced by a β-ketoester with a *gem*-dimethyl functionality at position 4. The *cis* substituents in C_{12} and C_{13} were introduced, as before,[4] by an intermolecular aldol reaction between the dienophile and the diene (Figure 1). For our model study, a racemic macrocycle was used.

Construction of macrocycle **3** began with the synthesis of dienophile **5** from ester−aldehyde **7** available in one step from commercial cyclopentene (Scheme 1).[5] Wittig olefination of the aldehyde provided the corresponding *trans* α,β-unsaturated aldehyde in 75% yield. Reduction of the aldehyde with $NaBH_4$ and silyl protection afforded the desired dienophile **5**.

The synthesis of diene **6** started with the monoprotection of 2,2-dimethylpropanediol with a THP group in 82% yield. Swern oxidation of the primary alcohol followed by Horner−Emmons reaction gave the *trans-trans* diene. Reduction of the ester with LAH and subsequent oxidation to the aldehyde afforded diene **6** in good yields.

Scheme 1. Synthesis of the Macrocycle[a]



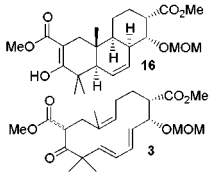
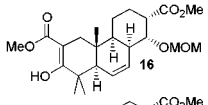
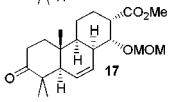
[a] (a) $PPh_3{=}C(CH_3)CHO$, C_6H_6, reflux, 75%; (b) $NaBH_4$, EtOH, 0 °C, 77%; (c) TBDPSCl, imidazole, 82%; (d) DHP, PTSA, THF/CH_2Cl_2 2:1, 82%; (e) DMSO, $(ClCO)_2$, CH_2Cl_2, −78 °C, then Et_3N, rt, 94%; (f) $(EtO)_2PO{-}CH_2CH{=}CHCO_2Et$, ^{n}BuLi, Et_2O, 98%; (g) LAH, Et_2O, 0 °C, 84%; (h) TPAP, NMO, MS 4 Å, CH_2Cl_2, 89%; (i) **5**, LDA, THF, −78 °C, then **6**, 85%; (j) MOMCl, DIPEA, CH_2Cl_2, 79%; (k) PPTS, MeOH, reflux, 77%; (l) TPAP, NMO, MS 4 Å, CH_2Cl_2, 73%; (m) AcOMe, LDA, THF, −78 °C, 81%; (n) Dess−Martin periodinane, 86%; (o) TBAF, THF, rt; (p) HCA, PPh_3, THF, −30 °C; (q) Cs_2CO_3, CsI, CH_3CN, reflux, slow addition 15 h, [2×10^{-3} M].

Having dienophile and diene in hand, both were connected by an aldol condensation to give a mixture of *syn* and *anti* adducts **9** and **10** in a 1:2 ratio which were separated by flash chromatography. The alcohol was protected as a MOM ether on both adducts and the THP removed to afford the corresponding primary alcohol. The β-ketoester connector was then elaborated by a sequence of oxidation, aldol condensation with methyl acetate, and subsequent oxidation to give β-ketoesters **11** and **12**. The TBDPS group was then removed, and the alcohols thus obtained were respectively transformed into the corresponding chlorides **13** and **14** in 81% yield with hexachloroacetone and triphenylphosphine in THF at −30 °C.[6]

The macrocyclization was then conducted by slow addition of the chloride to a refluxing acetonitrile solution of Cs_2CO_3 and CsI under high dilution, to yield the desired macrocycles **3** and **15** in 66 and 64% yields, respectively.

Now that the isomeric macrocycles **3** and **15** were synthesized, their behavior toward the TADA reaction was studied. As indicated in Table 1, only the TAC tricycle was obtained with the *cis* substituents in ring C.[7] The best result was obtained at 125 °C, yielding a mixture of TAC tricycle **16** along with the corresponding decarboxylated tricycle **17** in a 3:1 ratio.[8] With the *anti* substituents in ring C, no control was observed and a mixture of CAT and TAC tricycles was obtained, in keeping with results obtained in previous studies.[4]

Table 1. Diels−Alder Studies of TTT Macrocycles **3** and **15**

Substrate[a]	Temp. (°C)	Time (h)	Product isolates	Yield (%)
3	110	18	decomposition	0
3[b]	115	27	 **16**	57
			3	12
3[b]	125	18	 **16**	75
			 **17**	25
15[b]	125	18	2 Products observed	-

[a] All reactions were carried out in toluene. [b] 3 equiv of Et_3N was added.

On the basis of these results, an enantioselective synthesis of cassaine was envisaged. Cassaine **18** is a cardioactive alkaloid, isolated from *Erythrophleum guineense* bark, that

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(6) Magid, R. M.; Fruchey, O.; Johnson, W. L.; Allen, T. G. *J. Org. Chem.* **1979**, *44*, 359.

(7) For the X-ray crystal structure of compound **16**, see the Supporting Information.

(8) Triethylamine was added to be sure that the conditions of the TADA reaction were not acidic, even if it is not necessary.

has been known as inhibitor of Na^+, K^+-ATPase and to possess a pharmacological action similar to the digitalis glycosides.[9]

Our retrosynthetic analysis suggests that the TAT tricycle of cassaine, as shown in Figure 2, could come from TAC

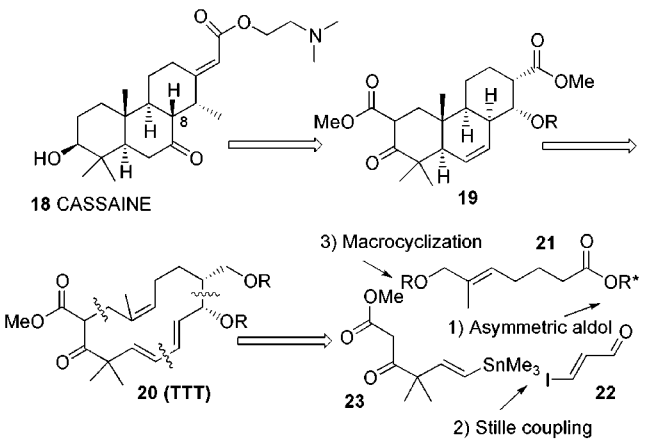
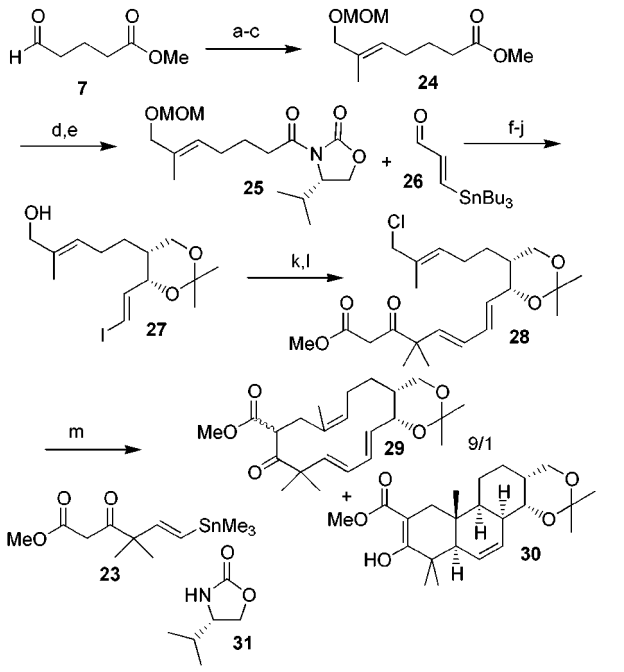


Figure 2. Retrosynthetic analysis of cassaine.

tricycle **19** after oxidation at C_7 and epimerization at C_8, with **19** being the TADA adduct obtained from triene **20**. An enantioselective synthesis of macrocycle **20** could be made, in a more convergent manner than in the model study, first by an asymmetric aldol reaction between dienophile **21** and aldehyde **22** and then by further elaboration of the diene by Stille coupling[10] with β-ketoester stannane **23**.[2a]

As shown in Scheme 2, the first two steps of the sequence were similar to those of the model study, with the alcohol protected as a MOM ether. Hydrolysis of ester **24** gave the corresponding carboxylic acid and then the Evans chiral auxiliary was introduced in a one-pot procedure to afford imide **25** in 86% yield.[11] The enantioselective aldol condensation was then performed in the presence of $TiCl_4$, TMEDA, and NMP with aldehyde **26**[12] to afford the corresponding aldol adduct in 55% yield.[13] Reduction of the imide with $NaBH_4$ without racemization[14] and then stannane/iodide exchange provided the diol in good yields. Deprotection of the MOM ether and protection of the two alcohols as an acetonide furnished iodide **27**. Stille coupling between iodide

Scheme 2[a]



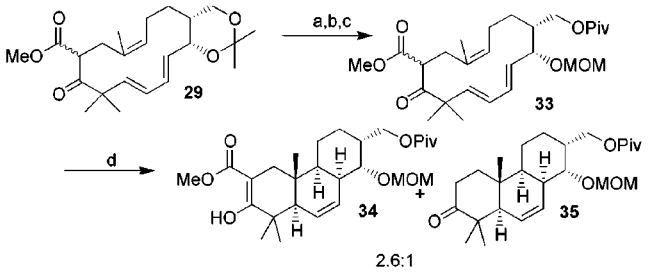
[a] (a) $Ph_3P{=}C(CH_3)CHO$, C_6H_6, reflux, 75%; (b) $NaBH_4$, MeOH, 0 °C, 77%; (c) $(MeO)_2CH_2$, LiBr, PTSA, 85%; (d) KOH, MeOH, 97%; (e) Et_3N, $(CH_3)_3CCOCl$, THF, −78 °C, then **31**, ^{n}BuLi, THF, −78 °C, 88%; (f) $TiCl_4$, TMEDA, NMP, CH_2Cl_2, −78 °C, 55%; (g) $NaBH_4$, THF/H_2O, 78%; (h) I_2, CH_2Cl_2, 97%; (i) HCl (concd), ^{i}PrOH, 55 °C, 16 h, 75%; (j) $(MeO)_2C(Me)_2$, PTSA, THF, 95%; (k) **23**, $Pd(CH_3CN)_2Cl_2$, DMF, 85%; (l) HCA, PPh_3, THF, −30 °C, 85%; (m) Cs_2CO_3, NaI, CH_3CN, reflux, slow addition 12 h, [2 × 10^{-3} M], 71%, **29/30** ratio 9/1.

27 and stannane β-ketoester **23** was then accomplished in DMF in 80% yield.[2a,10] The chlorination and macrocyclization were performed as previously described (vide supra) and with similar yields.

However, this time, TAC tricycle **30** was obtained in small quantities during the macrocyclization (**29/30** ratio 9:1), showing that the TADA reaction was even easier than in the model study.

The TADA reaction was tried at 125 °C (Table 2) with chiral macrocycle **29**, but surprisingly, it gave a mixture of

Scheme 3[a]



[a] (a) HCl 1N, THF, 0 °C, 1 h, 95%; (b) PvCl, 2,6-lutidine, CH_2Cl_2, 75%; (c) MOMCl, $(i\text{-Pr})_2$Net, CH_2Cl_2, 85%; (d) toluene, sealed tube, 125 °C, 100%, **34/35** ratio 2.6/1.

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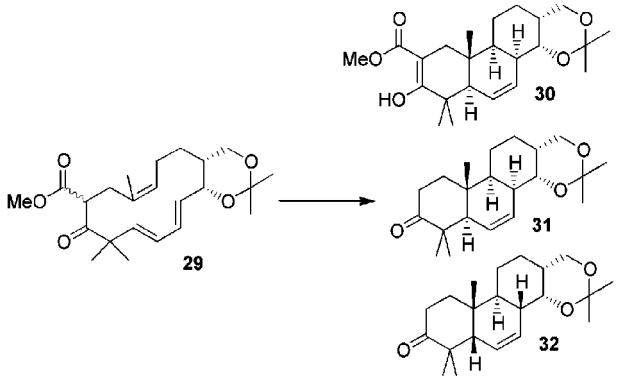
(14) Prashad, M.; Har, D.; Kim, H. Y.; Repic, O. *Tetrahedron Lett.* **1998**, *39*, 7067.

Table 2. TADA Studies on Macrocycle **29**



		yield (%)			
temp (°C)	time (h)	**30**	**31**	**32**	total yield (%)[a]
90	72	83			83
95	72	75		5	80
110	16	60	15	10	85
115	16	57	17	17	91
125	16	33	39	20	92

[a] All reactions were carried out in toluene.

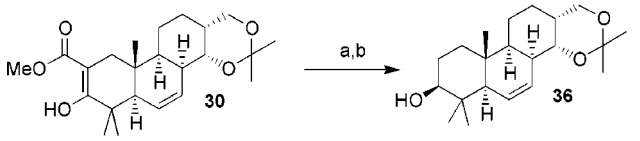
two TAC (one decarboxylated) and one CAT tricycle (TAC/CAT ratio 2.7:1). However, a brief temperature study showed that at 90 °C only the desired TAC tricycle **30** was formed. This result further indicates that the presence of the acetonide function allows the TADA reaction to occur at lower temperatures.

Knowing that without the acetonide only the TAC tricycle was observed and in order to better understand its role, the acetonide was cleaved (Scheme 3) and the primary alcohol protected with a pivalate while the secondary alcohol was protected as a MOM ether to give macrocycle **33**.

The TADA reaction of this macrocycle gave only the TAC ring junction at 125 °C, in agreement with the results previously obtained in the model study. This confirmed that the acetonide indeed lowers the transition state energy for both tricycles.

Pursuing the total synthesis of cassaine, elaboration of ring A was completed first by dealkoxycarbonylation[15] of tricycle **30** in quantitative yield (Scheme 4). Reduction of the ketone

Scheme 4[a]



[a] (a) NaOH 7%, MeOH/H_2O 3:2, 100%; (b) $NaBH_4$, MeOH, 0 °C, 95%.

at position 3 was accomplished with $NaBH_4$ in MeOH at 0 °C to give β epimer **36** (ratio β/α 95:5).[16,17]

In conclusion, we have synthesized interesting TAC tricycles by the TADA strategy, which can be used as key intermediate for the synthesis of cassaine. Further elaboration of the tricycles en route to the total synthesis of cassaine is in progress and will be reported in due course.

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Supporting Information Available: Experimental procedure and listing of spectral data (IR, ^1H and ^{13}C NMR, MS) for all synthetic compounds and X-ray crystal structure of compounds **16** and **36**. This material is available free of charge via the Internet at http//pubs.acs.org.

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(16) Jabin, I.; Revial, G.; Melloul, K.; Pfau, M. *Tetrahedron: Asymmetry* **1997**, *8*, 1101.
(17) For the X-ray crystal structure of tricycle **37**, see the Supporting Information.