

Transannular Diels-Alder Approach to the Synthesis of Momilactone A

Julie Germain and Pierre Deslongchamps*

Laboratoire de synthèse organique, Institut de pharmacologie,
Université de Sherbrooke, Sherbrooke (Québec), Canada J1H 5N4

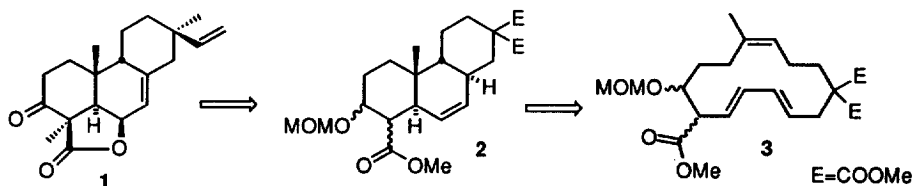
Received 8 March 1999; accepted 31 March 1999

Abstract. The application of the transannular Diels-Alder strategy on macrocyclic trienes having the *trans-trans-cis* olefin geometry led to *trans-syn-trans* tricycles which are advanced intermediates for the synthesis of natural products like Momilactone A. © 1999 Elsevier Science Ltd. All rights reserved.

In the past years, studies on transannular Diels-Alder (TADA) reaction have shown that 14-membered macrocycles having a *trans-trans-cis* (TTC) olefin geometry can lead to A.B.C.[6.6.6] tricycles having a *trans-syn-trans* (TST) ring junction stereochemistry.¹ Thus, in one step, two rings are generated and four asymmetric centers are created with high stereoselectivity. These results encouraged us to start the synthesis of natural products having this stereochemistry. For example, Momilactone A (**1**), isolated from rice husk,² was chosen as a target.

Retrosynthetic analysis demonstrates that Momilactone A can be synthesized in principle from tricycle TST **2**, which is in turn available from TTC macrocycle **3**. The formation of the macrocycle can be accomplished via a convergent strategy by aldol coupling of a diene and a dienophile followed by macrocyclization via a malonate connector.

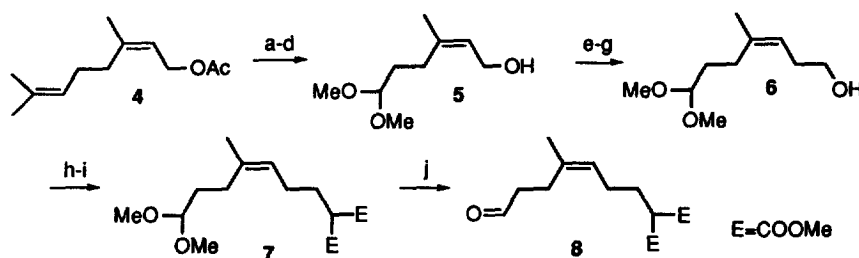
In this article, we wish to report the synthesis of tricycles **18a** and **18b** having the TST geometry which can be considered as key intermediates for the synthesis of **1**.



Scheme 1

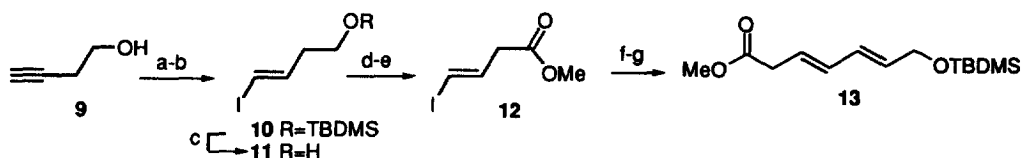
The construction of the *cis* dienophile started with the terminal olefin epoxidation of neryl acetate **4** with *m*-chloroperbenzoic acid in dichloromethane. The epoxide was opened with aqueous perchloric acid in DME and the resulting diol was cleaved in acidic solution with sodium metaperiodate to furnish the corresponding aldehyde.³ Exposure of this aldehyde to

an acidic methanolic solution of trimethylorthoformate and subsequent basic hydrolysis afforded alcohol **5** in 40% yield from neryl acetate. To complete the dienophile, one carbon homologation was necessary. Thus, functional group manipulations were accomplished by alcohol oxidation to aldehyde using TPAP-NMO, Wittig olefination with Ph_3PCH_2 and hydroboration of the terminal olefin with disiamylborane to give rise to the homologated product **6**. For the introduction of the malonate connector, alcohol **6** was transformed into an iodide⁴ and subsequent displacement of the latter by sodium dimethylmalonate provided compound **7**. Finally, the aldehyde dimethylacetal was deprotected using aqueous *p*-toluenesulfonic acid in acetone to give aldehyde **8**.



Scheme 2: a) *m*-CPBA, CH_2Cl_2 . b) HClO_4 , DME. c) NaIO_4 , H_2SO_4 , DME. d) HCl , $(\text{CH}_3\text{O})_3\text{CH}$, MeOH, then K_2CO_3 , 40%. e) TPAP, NMO, CH_2Cl_2 , 95%. f) Ph_3PMeI , PhLi , 75%. g) $(\text{Sia})_2\text{BH}$, THF, H_2O_2 -NaOH MeOH, 80%. h) Dead, PPh_3 , MeI, 85%. i) NaH , CH_2E_2 , THF-DMF, 70°C . j) APTS, acetone- H_2O , 79% for two steps.

Scheme 3 illustrates the synthesis of *trans-trans* diene **13**. Accordingly, protection of 3-butyn-1-ol **9** as TBDMS ether in standard conditions followed by hydrozirconation-iodination of the triple bond with Schwartz's reagent and iodine⁵ afforded exclusively *trans* vinylic iodide **10**. Desilylation of **10** was performed with acidic Dowex resin. The resulting alcohol **11** was oxidized using Jones reagent to a carboxylic acid which was esterified with chlorotrimethylsilane in MeOH.⁶ For the diene formation, Stille coupling⁷ was applied between iodide **12** and stannane $E\text{-Bu}_3\text{SnCH}=\text{CHCH}_2\text{OH}$ ⁸ to give a *trans-trans* diene which was protected as a TBDMS ether to yield **13**.

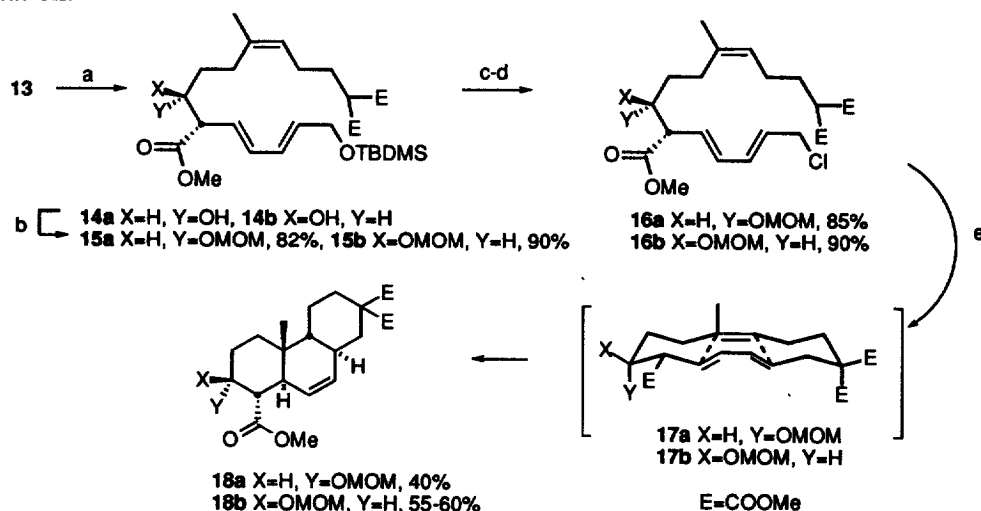


Scheme 3: a) TBDMSCl, imidazole, THF, 97%. b) $\text{Cp}_2\text{ZrClH-I}_2$, THF-Toluene, 88%. c) Dowex 50WX8, MeOH, 86%. d) Jones, 90%. e) TMSCl, MeOH, 84%. f) $E\text{-Bu}_3\text{SnCH}=\text{CHCH}_2\text{OH}$, $\text{PdCl}_2(\text{CH}_3\text{CN})_2$, 50%. g) TBDMSCl, imidazole, THF, 95%.

Having the diene and the dienophile in hand, these units were connected as shown in Scheme 4. Thus, aldol condensation of the ester anion of **13** with aldehyde **8** provided two

aldol adducts with an approximately 1.2:1 ratio for the *syn* and *anti* products in 88% global yield. The diastereomeric alcohols **14a**, **14b** were separated by silica gel chromatography. Both racemic diastereoisomers were investigated in order to find out which one would more conveniently lead to the synthesis of Momilactone. Once this is achieved, an appropriate asymmetric aldol condensation could be used to produce the natural product with complete relative and absolute stereochemical control.

Both alcohols were subjected to the same series of transformations. They were protected as MOM ethers, the TBDMS protecting group were removed in acidic medium and the resulting alcohols transformed into allylic chloride **16a**, **16b** respectively using Magid⁹ conditions. The key step of the synthesis was reached by slow addition of these allylic chlorides to a cesium carbonate suspension in refluxing acetonitrile under high dilution. The macrocyclisation-cycloaddition took place in a single step to afford the TST tricycles **18a** and **18b** (yields for the two steps: 40% and 55-60% respectively). The specific formation of TST tricycles **18a** and **18b** is the result of *endo* transition states **17a** and **17b** having each a chair-boat-chair conformation with the ring A carbomethoxy group in a pseudo-equatorial orientation.



Scheme 4: a) LDA, THF, -78°C, then 8, -78°C, 88%. b) MOMCl, DIPEA, CH₂Cl₂. c) Dowex 50WX8, MeOH. d) HCA, PPh₃, THF, -40°C. e) Cs₂CO₃, CH₃CN, reflux.

Preliminary results towards Momilactone showed that partial basic hydrolysis of malonate ester **18b** gave mainly the equatorial monoacid **19**. X-ray diffraction analysis¹⁰ of compound **19** rigorously established the proposed structure and relative stereochemistry. In principle, a series of functional group manipulations from either **18a** and **18b** should lead to the total synthesis of racemic Momilactone A.

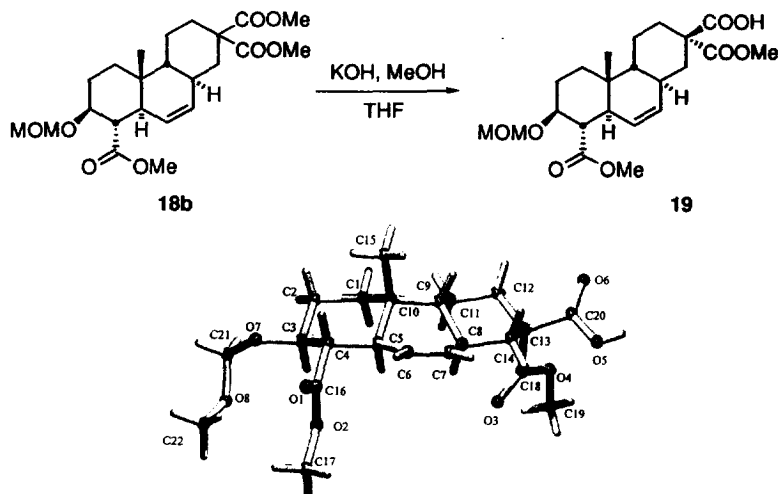


Figure 1. X-ray crystal structure of monoacid 19

In conclusion, we have synthesized interesting TST tricycles by the TADA strategy which are advanced intermediates towards the synthesis of Momilactone. Work toward the completion of the synthesis is now in progress.

Acknowledgments

This research was supported by the Natural Sciences and Engineering Research Council of Canada (NSERCC), Ministère de l'Enseignement Supérieur et de la Sciences (F.C.A.R, Québec). J. Germain thanks Université de Sherbrooke for financial support. We are also thankful to Marc Drouin, Université de Sherbrooke, for carrying out the X-ray structural determination of monoacid 19.

References

- [1] (a) Deslongchamps, P. *Aldrichimica Acta* **1991**, *43*, 24. (b) Lamothe S.; Ndibwami, A.; Deslongchamps, P. *Tetrahedron Lett.* **1988**, 1639, 1641. (c) Ndibwami, A.; Lamothe, S.; Soucy, P.; Golstein, S.; Deslongchamps, P. *Can. J. Chem.* **1993**, *71*, 714.
- [2] (a) Kato, T.; Kabuto, C.; Sasaki, N.; Tsunagawa, M.; Aizawa, H.; Fujita, K.; Kato, Y.; Kitahara, Y. *Tetrahedron Lett.* **1973**, 3361. (b) Cartwright, D.W.; Langcake, P.; Pryce, R.J.; Leworthy, D.A.; Ride, J. P. *Phytochemistry* **1981**, 535.
- [3] Jenn, T.; Heissler, D. *Tetrahedron* **1998**, 107.
- [4] Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, *59*, 2100.
- [5] Schwartz, J.; Labinger, J.A. *Angew. Chem. Int. Ed. Engl.* **1976**, 333.
- [6] Nakao, R.; Oka, K.; Fukumoto, T. *Bull. Chem. Soc. Jpn* **1981**, *54*, 1267.
- [7] Stille, J.K.; Groh, B.L. *J. Am. Chem. Soc.* **1987**, *109*, 813.
- [8] Lipshutz, B.; H.; Lindsley, C. *J. Am. Chem. Soc.* **1997**, *119*, 4555.
- [9] Magid, R.M.; Fruchey, O.; Johnson, W.L.; Allen, T.G. *J. Org. Chem.* **1979**, *44*, 359.
- [10] Crystallographic data of compound 19 (CCDC 115341) were deposited at the Cambridge Crystallographic Data Centre.