Synthesis of a 14β-Hydroxysteroid Using the Transannular Diels-Alder Strategy

L. Ouellet, P. Langlois, Pierre Deslongchamps*

Laboratoire de synthèse organique, Département de chimie, Faculté des sciences, Université de Sherbrooke, Sherbrooke (QC) Canada J1K 2R1

Fax: (819) 821-7910; e-mail: dlnchamp@structure.chimie.usherb.ca

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Abstract: Macrocyclic TCC triene **1**, generated by an intramolecular alkylation of a β-ketoester on a π-allylpalladium complex followed by dehydrogenation, underwent a highly stereoselective transannular Diels-Alder reaction affording the tetracyclic compound **2** in an excellent yield.

Since the early years of modern pharmacology the cardiac glycosides (Figure 1), usually called cardenolides, have been used for the treatment of congestive heart failure. The main biological activity[1] of these substances is to increase the strength of the myocardic contractions. Unfortunately they are very toxic since the therapeutic dose could be as close as 60% of the lethal dose, a fact that generates interest in synthesizing potent analogs without this toxicity.

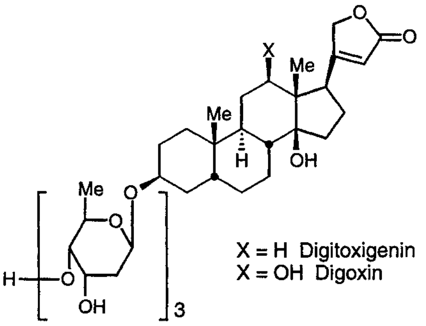
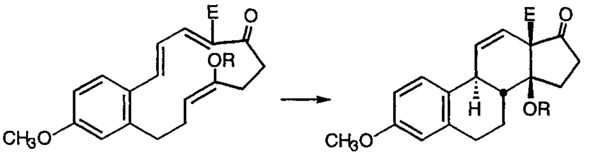


Figure 1

The particular structure of these steroids comes from the *cis* C-D ring fusion, a tertiary hydroxyl group at C-14 and a β-oriented butenolide at C-17. Recently, a total synthesis of (+)-digitoxigenin[2] and a strategy for the total synthesis of cardenolides[3] were reported showing the renewed interest for these compounds.

Results from our laboratory[4,5] clearly demonstrated that the transannular Diels-Alder reaction of a 13-membered macrocycle having a *trans-cis* diene and a *cis* dienophile gave the BCD rings of the cardenolides with the correct *trans-syn-cis* (TSC) stereochemistry. We have undertaken the synthesis of a 13-membered macrocyclic triene **1** (Scheme 1) with a *trans-cis-cis* (TCC) geometry and an aromatic A ring which leads, after the Diels-Alder reaction, to the tetracycle **2**, a precursor of 14-β-hydroxysteroids. We wish to report this work.

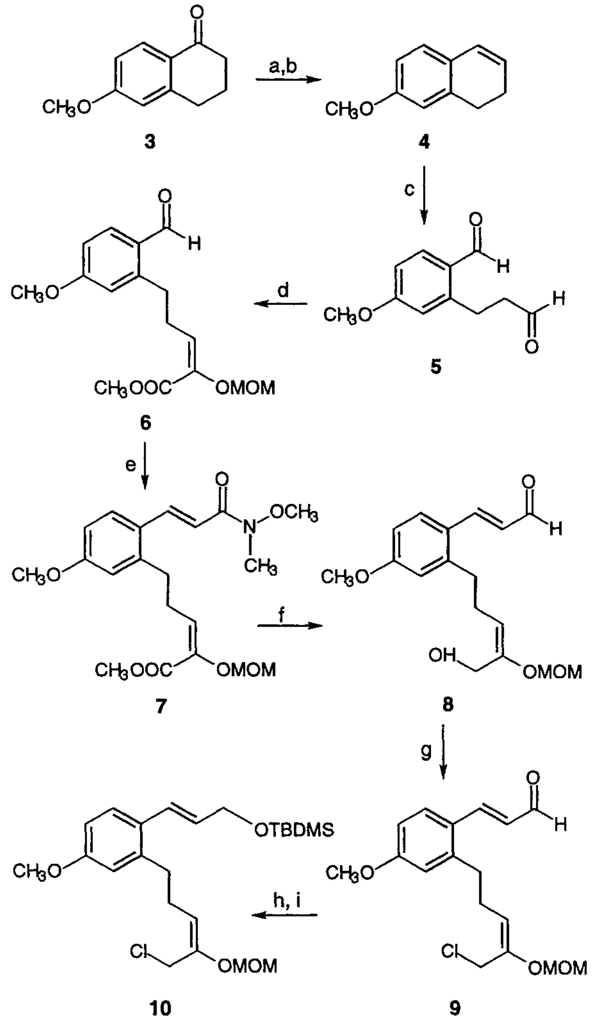


1 **2**

E = $COOCH_3$
R = MOM

Scheme 1

Reduction[6] of 6-methoxytetralone followed by dehydration of the resulting alcohol gave the synthon **4** in 88% yield for the two steps (Scheme 2). Ozonolysis of the double bond followed by a reductive work-up yielded the unstable dialdehyde **5** which, without purification,



Scheme 2. (a) $LiAlH_4$, THF, -78°C, 1 h (b) TsOH, C_6H_6, $-H_2O$, 88% (c) O_3, MeOH, -78°C; then DMS, r.t. (d) *n*-BuLi, 0°C, $(CH_3O)_2P(O)CH(OMOM)COOCH_3$, THF, 64% (e) *n*-BuLi, $(CH_3CH_2O)_2P(O)CH_2C(O)N(OCH_3)CH_3$, 0°C, THF, 85% (f) $LiAlH_4$, THF, -78°C to 0°C, 78% (g) MsCl, Et_3N, CH_2Cl_2, 0°C, then HMPA, LiCl, r.t., 85% (h) $NaBH_4$, MeOH, r.t., 99% (i) TBDMSCl, Imidazole, THF, r.t., 84%.

was condensed with the anion of 2-methoxymethyloxy-2-trimethylphosphonoethanoate[7-10] affording the unsaturated ester **6** in 64% yield with a good selectivity (E/Z 20:1). The two isomers were separated by flash-chromatography. A second Emmons-Horner olefination was performed on the aldehyde **6** using diethyl(*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate[11] giving the Weinreb amide **7** in 85% yield with excellent selectivity (E/Z >90:1). Reduction of the amide and the ester was achieved with lithium aluminum hydride at low temperature affording the aldehyde-alcohol **8** in 78% yield. The alcohol was transformed into the chloride **9** using the Collington-Meyers method.[12] The aldehyde was then reduced to the alcohol with sodium borohydride and protection of this alcohol with *t*-butyldimethylsilylchloride gave **10** in 68% yield for three steps.

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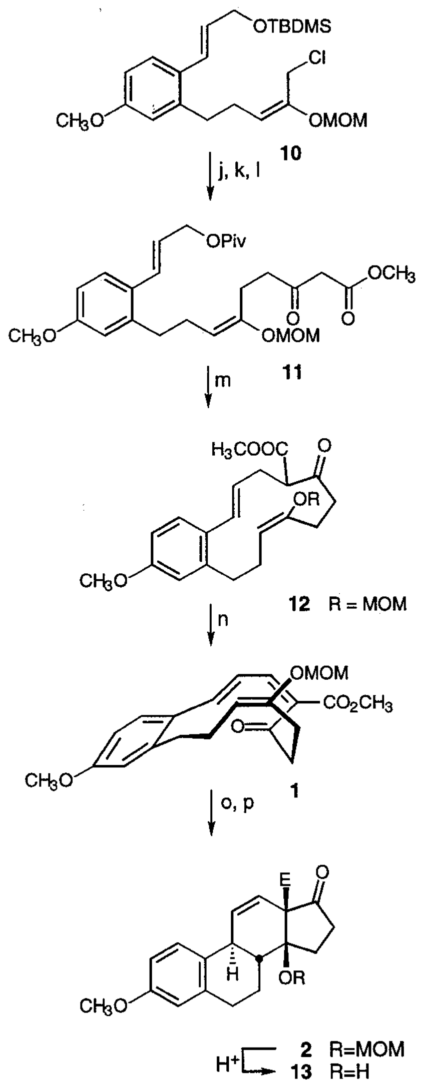

Scheme 3. (j) NaH, *n*-BuLi, $CH_3C(O)CH_2C(O)OCH_3$, THF, 0°C, 84% (k) TBAF, THF, r.t., 80% (l) PivCl, 2,6-lutidine, CH_2Cl_2, 0°C, 89% (m) *N,O*-bis(trimethylsilyl)acetamide, THF, reflux, then $[(Ph)_3P]_4Pd$, $(Ph)_2P(CH_2)_3P(Ph)_2$, THF, reflux, 67% (n) $(PhSeO)_2O$, Et_3N, CH_2Cl_2, r.t., 91% (o) Et_3N, xylene, reflux, 11 h, 91% (p) HCl, MeOH, r.t., 86%.

Reaction of the dianion[13] of methyl acetoacetate with the chloride **10** afforded the corresponding β-ketoester (Scheme 3). Deprotection of the silyl group with fluoride ions followed by reprotection of the alcohol as a pivaloate ester gave **11** in 81% yield for the two steps. In only 12 steps, we have obtained the macrocyclic precursor **11**. At this stage, all the carbons needed for the macrocycle are present. The macrocyclisation was performed by the reaction of the trimethylsilyl enol ether of the β-ketoester on a π-allyl palladium complex.[14] The corresponding β-ketoester macrocycle **12** was obtained in 67% yield with no trace of O-alkylated product. Introduction of the second double bond of the diene was accomplished by a dehydrogenation with benzeneselenenic anhydride[15] affording the macrocyclic triene **1** having the *trans-cis-cis* (TCC) geometry in 91% yield. A single elimination product was obtained, the *cis* double bond produced is probably a result of ring effect since the macrocycle would tolerate with difficulty the strain resulting from an additional *trans* double bond. The transannular Diels-Alder reaction proved indirectly the geometry of the diene. Heating the triene **1** for 12 h in refluxing xylene afforded a single product, the tetracycle **2** in an excellent 80% yield. Finally, deprotection of the methoxymethylether with acid gave the tetracycle **13**, which was recrystallized allowing X-ray diffraction for structural determination (Figure 2). The predicted TSC stereochemistry was thus confirmed.

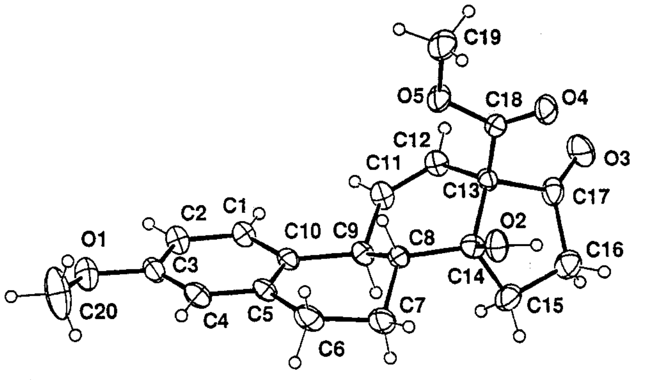

Figure 2. ORTEP drawing of **2**.

The efficiency and the power of the transannular Diels-Alder reaction for the construction of polycyclic compounds with unusual ring junction stereochemistry is well illustrated by this example in which a 14β-hydroxysteroid is obtained with the formation of four asymmetric centers in one step. Work is currently carried out to create a chiral version of this approach and to modify the existing functional groups in order to find new access to analogs of digitoxine and other cardenolides[16].

Acknowledgements

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(16) Previous scientific work on cardenolides can be found in references 2 and 3.

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