JOC Article

New Strategy for Convergent Steroid Synthesis

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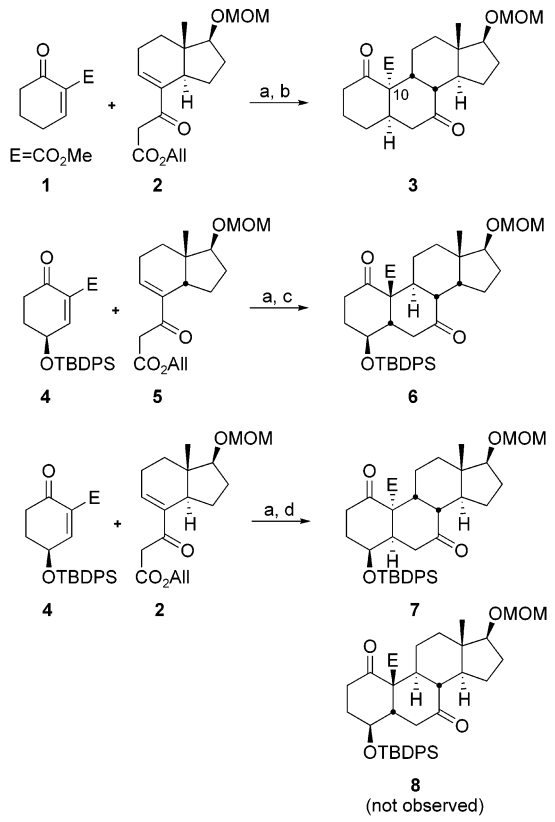
We published recently our results on a new and convergent synthesis of natural steroids. The strategy was based on a cycloaddition reaction of Nazarov reagents **2** and **5** with cyclohexenones **1** and **4**. In this paper we report results that deal with the synthesis of two new bicyclic Nazarov reagents (**13** and **19**) and their cycloaddition with two cyclohexenones (**1** and **4**). These new results constitute an important improvement concerning the versatility of the strategy since tetracycles having the stereochemistry found in natural steroids are now available.

Introduction

Steroids constitute an important class of natural products, which has attracted the attention of organic chemists worldwide. These compounds have numerous therapeutic effects,[1] and new strategies for their synthesis are always welcomed. A lot of strategies have been developed for the synthesis of steroids; only a few start with a CD bicyclic building block, but are not convergent.[2] Recently, we reported our results regarding a new and efficient strategy for steroid synthesis,[3] involving the cycloaddition of bicyclic Nazarov reagents **2** and **5** and the cyclohexenones **1** and **4**, respectively, followed by a regioselective decarboxylation (Scheme 1). This new strategy gave tetracyclic compounds **3** and **6** with complete diastereoselectivity at four new chiral centers. The stereochemistries obtained at C-5 and C-10 (steroid numbering) were opposite in the two series. It was concluded that the configuration of the angular methyl group in **2** directed the cycloaddition approach in the first case, while the stereochemistry of the second case was controlled by the chirality of the OTBDPS group of cyclohexenone **4**. Nazarov reagent **2** was then condensed with **4** to give exclusively **7**. Since none of the other isomer (**8**) was observed, we showed that the configuration of the angular methyl group of **2** prevailed over that of cyclohexenone **4** (Figure 1; approach B is favored over approach A). Since the stereochemistry normally found in natural steroids was not observed (cf. **8**), we have continued our study with new Nazarov reagents to improve the versatility of our strategy. We report the synthesis of two new bicyclic Nazarov reagents (**13** and **19**) and the results of their cycloaddition with the two cyclohexenones **1** and **4**.[4,5]

SCHEME 1[a]



[a] Reagents and conditions: (a) Cs_2CO_3, CH_2Cl_2; (b) $Pd(PPh_3)_4$, morpholine, THF, 87% (two steps); (c) $Pd(PPh_3)_4$, morpholine, THF, 60% (two steps); (d) $Pd(PPh_3)_4$, morpholine, THF, 50% (two steps).

Results and Discussion

The Hajos−Parrish ketone **9**[6] was selected as the starting material for the synthesis of the Nazarov reagent

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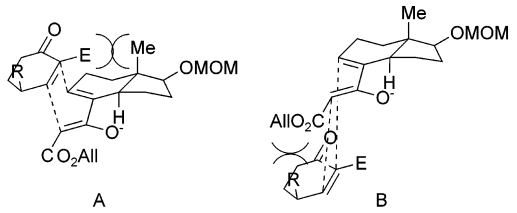
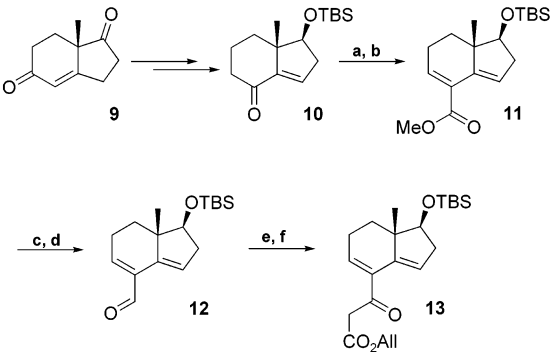


FIGURE 1. Comparison of the cycloaddition approaches for the reaction of **2** with **4**. When R = OTBDPS, approach B is favored over approach A.

SCHEME 2[a]

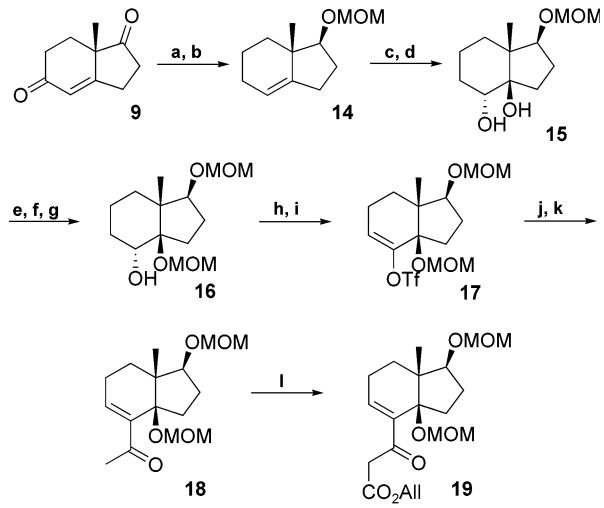


[a] Reagents and conditions: (a) (i) LDA, THF, −78 °C, (ii) Comins' reagent, −30 °C, 73%; (b) CO (1 atm), $PdCl_2(PPh_3)_2$, K_2CO_3, MeOH, DMF, 60%; (c) DIBAL, CH_2Cl_2, −78 °C, 86%; (d) Dess−Martin periodinane, CH_2Cl_2, 86%; (e) (i) LDA, allyl acetate, THF, −78 °C, (ii) **12**, −78 °C, 89%; (f) Dess−Martin periodinane, CH_2Cl_2, 100%.

having an unsaturation in the five-membered ring (**13**) (Scheme 2). The transformation of the diketone **9** to the enone **10** was already reported in the literature.[7] The α,*β*-unsaturated ester **11** was obtained by trapping the kinetically favored enolate with the Comins reagent (*N*-(5-chloro-2-pyridyl)triflimide)[8,9] to form the enol triflate, followed by a carbonylation reaction.[10] The α,*β*-unsaturated ester **11** obtained was then reduced to the alcohol and oxidized to the α,*β*-unsaturated aldehyde **12**.[11] Allyl acetate lithium enolate was added to **12**, and the resulting alcohol was oxidized with the Dess−Martin periodinane,[11] affording Nazarov reagent **13**.

To compare the cycloaddition, we also synthesized the Nazarov reagent **19** with a protected hydroxyl group at the ring junction (Scheme 3). The synthesis of **19** involved reduction[12] of ketone **9**[6] followed by protection, affording the MOM-protected alcohol **14**.[3] The *β*-epoxide was obtained using dimethyldioxirane in acetone,[13] which was then opened under basic conditions to give the diol **15**.[13] A sequence of protection and deprotection furnished compound **16** in which the more hindered tertiary hydroxyl group was protected. The secondary alcohol was then oxidized to the ketone,[14] and the enolate of the

SCHEME 3[a]



[a] Reagents and conditions: (a) $NaBH_4$, TFA, CH_3CN, 73%; (b) MOMCl, $(i\text{-Pr})_2EtN$, CH_2Cl_2, 82%; (c) DMDO/acetone, CH_2Cl_2, 71%; (d) KOH, H_2O, DMSO, 120 °C, 81%; (e) TMSCl, Et_3N, THF; (f) MOMCl, $(i\text{-Pr})_2EtN$, DMAP, CH_2Cl_2, 100% (two steps); (g) TBAF, THF, 86%; (h) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, 100%; (i) (i) LDA, THF, −78 °C, (ii) Comins' reagent, −30 °C, 92%; (j) $CH_2{=}C(SnBu_3)OEt$, $PdCl_2(PPh_3)_2$, LiCl, DMF, 60 °C; (k) oxalic acid, DMF, 50% (two steps); (l) (i) LiHMDS, THF, −78 °C, (ii) $NCCO_2$-allyl, −30 °C, 87%.

ketone was trapped with Comins' reagent[8,9] to afford the enol triflate **17**. A Stille coupling reaction was performed,[15,16] and the resulting enol ether was hydrolyzed to the methyl ketone **18**. Finally the lithium enolate of this methyl ketone reacted with allyl cyanoformate[17] to afford the Nazarov reagent **19**.

Having both Nazarov reagents **13** and **19**, we studied their cycloaddition reaction with cyclohexenones **1** and **4**.[4,5] The reaction of Nazarov reagent **13** and cyclohexenone **1** (Scheme 4) afforded, after selective decarboxylation,[18] only the *cis-anti* tetracyclic compound **20**. It should be noted that the unsaturation in the five-membered ring isomerized to become conjugated with the ketone. The structure of this tetracyclic compound **20** was proved by X-ray diffraction analysis[19] of compound **22**, a derivative of **20**. We believe that the anionic cyclization process takes place either via a highly asynchronous Diels−Alder reaction or by two consecutive Michael additions where the first step would be reversible. The cycloaddition thus proceeds from the less hindered face of the Nazarov reagent (the α face) probably due to the strong steric interaction created by the tertiary methyl group (Figure 2; approach B is favored over approach A). We then tried to force the cycloaddition to proceed on the other face of the Nazarov reagent (the *β* face) by using the chiral cyclohexenone **4**[5] (Scheme 4). The protected hydroxyl group of compound **4** blocks the *β* face of the

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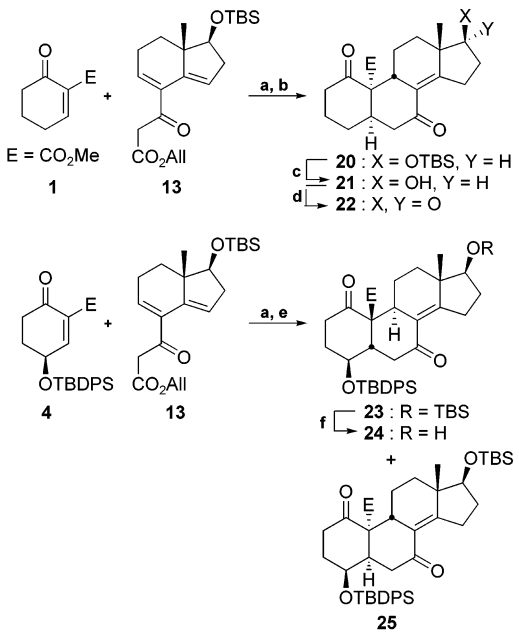
(19) We thank Mr. Andreas Decken for the X-ray diffraction analysis.

SCHEME 4[a]



[a] Reagents and conditions: (a) Cs_2CO_3, CH_2Cl_2; (b) $Pd(PPh_3)_4$, morpholine, THF, 60% (two steps); (c) concentrated HCl, MeOH, reflux, 85%; (d) Dess−Martin periodinane, CH_2Cl_2, 50%; (e) $Pd(PPh_3)_4$, morpholine, THF, 17% (two steps); (f) concentrated HCl, MeOH, reflux, 85%.

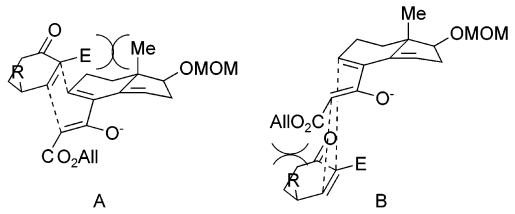
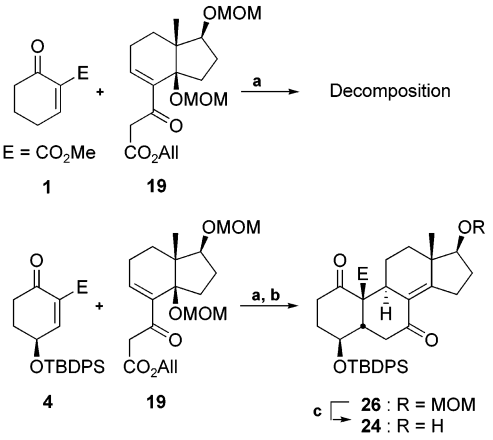


FIGURE 2. Comparison of the cycloaddition approaches for the reaction of **13** with **1** or **4**. When R = H, approach B is favored over approach A. When R = OTBDPS, approach A is slightly favored over approach B.

cyclohexenone and favors an approach of the β face of the Nazarov reagent for the cycloaddition. When the cycloaddition was carried out, a mixture of compound **23** and another minor compound (approximately 4:1) was obtained with low yields due to important decomposition. We have assumed that the minor compound is **25** on the basis of the result of the cycloaddition between **1** and **13**. This difficult and noncompletely stereoselective cyclization can be explained by the strong steric interactions created in both approaches. The major compound (**23**) results from the cycloaddition on the β face of the Nazarov reagent to avoid the steric interaction created by the protected alcohol in **4** (Figure 2; approach A is slightly favored over approach B). The structure of the tetracyclic compound **23** was proved by X-ray diffraction analysis[19] of its derivative compound **30** (Scheme 6).

The cycloaddition of the Nazarov reagent **19** was then studied (Scheme 5). When the cycloaddition of the Nazarov reagent **19** with the cyclohexenone **1** was carried out, only decomposition was observed. The low reactivity

SCHEME 5[a]



[a] Reagents and conditions: (a) Cs_2CO_3, CH_2Cl_2; (b) $Pd(PPh_3)_4$, morpholine, THF, 55% (two steps); (c) concentrated HCl, MeOH, reflux, 85%.

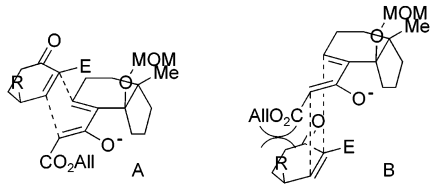
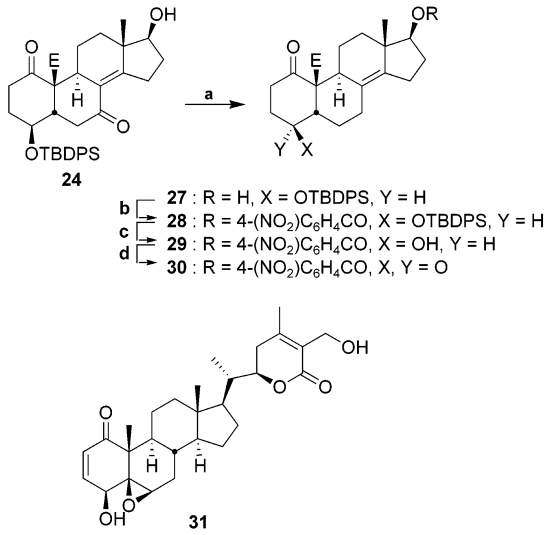


FIGURE 3. Comparison of the cycloaddition approaches for the reaction of **19** with **4**. When R = OTBDPS, approach A is favored over approach B.

of the cyclohexenone **1** and the low stability of the Nazarov reagent **19** could explain this result. In another attempt, when we tried the cycloaddition of **19** with the more reactive cyclohexenone **4**,[5] we obtained only the *cis-anti* tetracyclic compound **26**. The structure of tetracyclic compound **26** was proven by X-ray diffraction analysis[19] of its derivative **30** (Scheme 6). It should be noted that, instead of obtaining the desired tetracycle with a protected tertiary hydroxyl group, we ended up with enone **26** due to an elimination reaction. The fact that cycloaddition proceeded only on the β face of the Nazarov reagent **19** can be explained by the steric interaction created by the OTBDPS group on the cyclohexenone **4** and less steric interaction from the angular methyl group in **19** by comparison with that of **13** or **2** (Figure 3; approach A is favored over approach B). In fact, Nazarov reagent **19** reacts like Nazarov reagent **5** having the same *cis* CD ring junction. Selective deprotection on compounds **26** (Scheme 5) and **23** (Scheme 4) afforded exactly the same tetracyclic compound (**24**).

Other reactions were also performed on compound **24** to obtain a crystalline compound for X-ray diffraction analysis (Scheme 6). We first tried to reduce the double bond under the usual conditions. Instead of hydrogenating the double bond under the reaction conditions used, the ketone function of the enone moiety was hydrogenolyzed to a methylene group. Protection of the free alcohol followed by selective desilylation of the TBDPS group followed by oxidation furnished crystalline compound **30** whose structure was established by X-ray diffraction analysis.[19]

SCHEME 6[a]



[a] Reagents and conditions: (a) H_2 (1 atm), Pd/C*, EtOH, 76%; (b) 4-nitrobenzoyl chloride, pyridine, DMAP, CH_2Cl_2, 94%; (c) HF·pyridine, THF, 90 °C, 65%; (d) Dess−Martin periodinane, CH_2Cl_2, 81%.

Conclusion

In conclusion, we have executed successfully the cycloaddition reactions using the Nazarov reagents **13** and **19**. Utilizing this novel protocol, the synthesis of various steroidal backbones has been achieved. The cycloaddition of Nazarov reagent **19** and cyclohexenone **4** allowed us to obtain with complete stereocontrol the important tetracyclic compound **26**. The β configuration of the ester at C-10 and the methyl at C-13 corresponds to the chirality found in various natural steroids. The results presented here broaden the versatility of this synthetic approach and demonstrates that this methodology could be used for the synthesis of various natural products. Tetracyclic compound **6** is suitable for the synthesis of steroids with a CD *cis* ring junction, and tetracyclic compound **26** could be used for steroids having a *trans* or a functionalized CD ring junction.[20] For example, withaferin A (**31**)[21] (Scheme 6) is a natural steroid that could be achieved using our methodology. The total syntheses of natural products involving this novel protocol are presently in progress in our laboratory and will be reported in due course.

Acknowledgment. A research chair in organic chemistry to P.D. from BioChem Pharma Inc. is deeply appreciated. Fellowships FCAR-Quebec and NSERC-Canada to O.L. are highly appreciated.

Supporting Information Available: Experimental procedures and characterization data for all new compounds, ^{1}H NMR spectra for all compounds, and X-ray crystal structure data for compounds **22** and **30**. This material is available free of charge via the Internet at http://pubs.acs.org. The following crystal structures have been deposited at the Cambridge Crystallographic Data Centre: **22** (CCDC 196332) and **30** (CCDC 196331).

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