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Nazarov Reagents for Convergent and Expedient Synthesis of New Steroids

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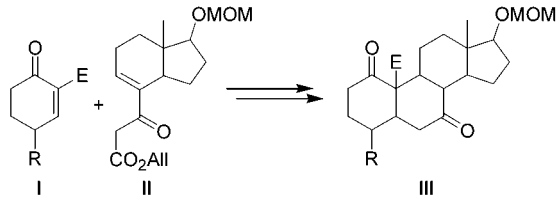
ABSTRACT



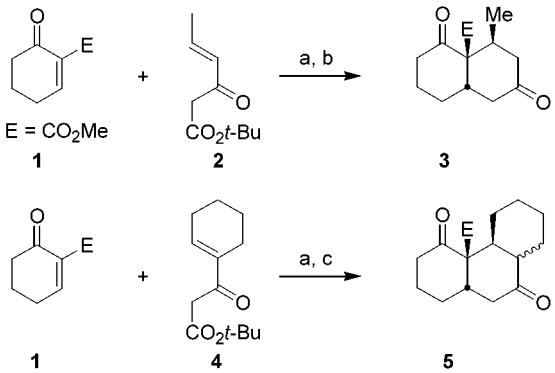
A new methodology for the convergent synthesis of tetracyclic compounds was developed. Two new bicyclic Nazarov reagents of type II were synthesized, and their cycloaddition with 2-carbomethoxy-2-cyclohexenone I was studied. This cycloaddition afforded new interesting steroidal backbones.

Several years ago, our laboratory discovered a new stereocontrolled synthesis of decalins. It was found that the reaction between cyclohexenone **1** and Nazarov reagent **2** afforded the *cis*,*cis*-decalin **3** in good yield and with very good diastereoselectivity, after selective decarboxylation of the *tert*-butyl ester (Scheme 1).[1,2] Cyclic Nazarov reagent **4** was also studied,[2] opening the way to a new methodology for the synthesis of tricyclic compounds.

We recently decided to synthesize some new bicyclic Nazarov reagents and study their reactions with cyclohexenone **1**. This reaction could be the key step in a new steroid synthesis via a convergent approach starting with a CD bicyclic building block. In this Letter we wish to report the synthesis of the two new Nazarov reagents **11** and **15**, having respectively a *trans* and a *cis* ring junction. We also report their cycloaddition with the cyclohexenones **1** and **20**.

The Hajos−Parrish ketone **6**[3] was selected as starting material for the synthesis of Nazarov reagent **11** having a *trans* ring junction (Scheme 2). After selective reduction of the unconjugated ketone and subsequent protection of the alcohol as a methoxy methyl ether, an acylation was performed with magnesium methyl carbonate at the α position of the α,*β*-unsaturated ketone **7**.[4] The resulting acid was esterified with diazomethane, and compound **8** having the *trans* ring junction was obtained after catalytic hydro-

Scheme 1[a]



[a] Reagents and conditions: (a) Cs_2CO_3, $CHCl_3$, rt; (b) p-TsOH, C_6H_6, reflux, 69% (two steps); (c) CF_3CO_2H, C_6H_6, reflux, 66% (two steps).

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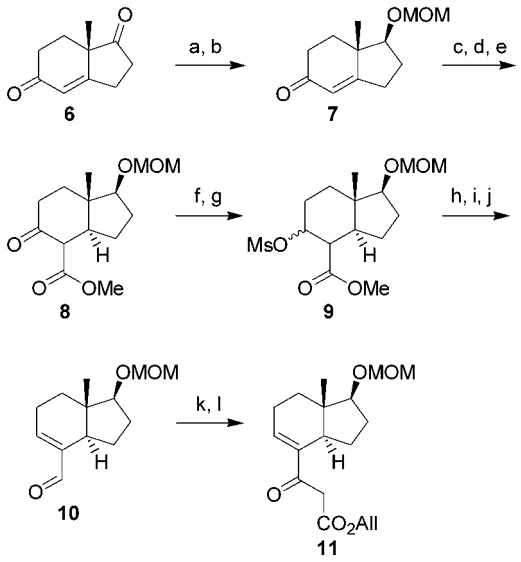
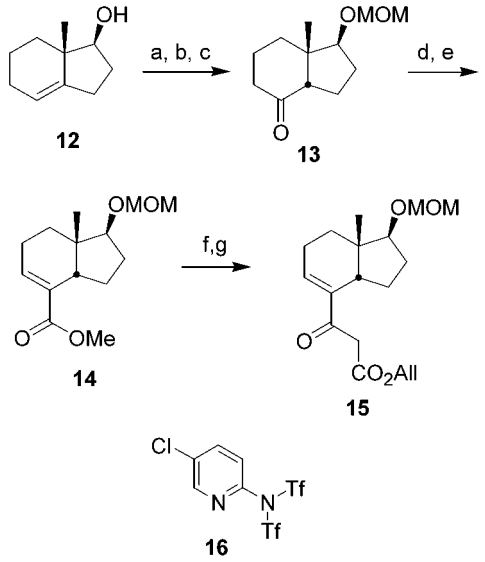
Scheme 2[a]



[a] Reagents and conditions: (a) $NaBH_4$, CH_2Cl_2, MeOH, −78 °C, 90%; (b) MOMCl, $(i\text{-Pr})_2EtN$, CH_2Cl_2, rt, 61%; (c) $MeOCO_2Mg\text{-}OMe\cdot xCO_2$/DMF, DMF, 125 °C; (d) CH_2N_2, Et_2O, 0 °C; (e) H_2 (1 atm), $Pd/BaSO_4$, EtOH, rt; (f) $NaBH_4$, MeOH, −78 °C, 49% (four steps); (g) MsCl, Et_3N, CH_2Cl_2, −5 °C, 93%; (h) DIBAL, Et_2O, −78 °C, 65%; (i) Dess−Martin periodinane, CH_2Cl_2, rt, 91%; (j) NaI, Pyridine, DMF, 100 °C, 97%; (k) i. LDA, allyl acetate, THF, −78 °C, ii. **10**, −78 °C, 88%; (l) Dess−Martin periodinane, CH_2Cl_2, rt, 96%.

Scheme 3[a]



[a] Reagents and conditions: (a) MOMCl, $(i\text{-Pr})_2EtN$, CH_2Cl_2, rt, 82%; (b) BH_3/THF, THF, rt, 71%; (c) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 79%; (d) i. LDA, THF, −78 °C, ii. Comins' reagent (**16**), −30 °C, 60%; (e) CO (1 atm), $PdCl_2(PPh_3)_2$, K_2CO_3, MeOH, THF, rt, 67%; (f) i. LDA, *tert*-butyl acetate, THF, −78 °C, ii. **14**, 0 °C; (g) AllylOH, DMAP, toluene, reflux, 46% (two steps).

genation. This reaction is known to give the *trans* junction on similar compounds.[4] The ketone of the β-keto-ester was reduced and converted into mesylate **9**. The ester was then reduced using diisobutylaluminum hydride, and the resulting alcohol was oxidized with Dess−Martin periodinane.[5] At this point, basic conditions were used to eliminate the mesylate, affording the α,β-unsaturated aldehyde **10**.[6] Attempts to eliminate the mesylate on compound **9** gave low yield and selectivity. An aldol reaction was performed on the unsaturated aldehyde **10** with the anion of allyl acetate to obtain the β-hydroxy ester. Finally, oxidation of the alcohol with Dess−Martin periodinane[5] afforded Nazarov reagent **11**.

To compare its reactivity, the Nazarov reagent **15** with a *cis* ring junction was synthesized using alcohol **12** as starting material (Scheme 3). Alcohol **12** was obtained in three steps from Hajos−Parrish ketone **6**.[7] After protection of the alcohol as a methoxy methyl ether and hydroboration on the unsaturation, the resulting *cis* ring junction alcohol[7] was oxidized to the ketone **13**.[8] The kinetically formed enolate was trapped in situ by Comins' reagent,[9,10] and a one-carbon homologation was then performed on the enol triflate using a carbonylation reaction.[11] A Claisen condensation was then performed on the ester **14** with the anion of *tert*-butyl acetate, and Nazarov reagent **15** was obtained by transesterification using the conditions developed by Taber.[12]

With Nazarov reagents **11** and **15** in hand, cycloaddition studies began (Scheme 4). The reaction was first performed with cyclohexenone **1** and Nazarov reagent **11**. This reaction afforded, after selective decarboxylation,[13] only the *cis-anti-cis-anti-trans* tetracyclic compound **17**. The structure of the tetracycle was proved by X-ray diffraction analysis[14] of its nitrobenzoate derivative **19**. We believe that the anionic cyclization process takes place either via a highly asymmetric Diels−Alder reaction or by two consecutive Michael additions where the first step would be reversible. In this manner, the cycloaddition can occur on the α face of Nazarov reagent **11** to avoid a steric interaction with the C-13 (steroid numbering) tertiary methyl group (Figure 1, approach **B** was favored over **A**).

We then tried to force the reaction to proceed on the other face of the Nazarov reagent by utilizing the chiral cyclohexenone **20** having a protected alcohol in position 4 (Scheme 4). This alcohol partially blocks the β face of the

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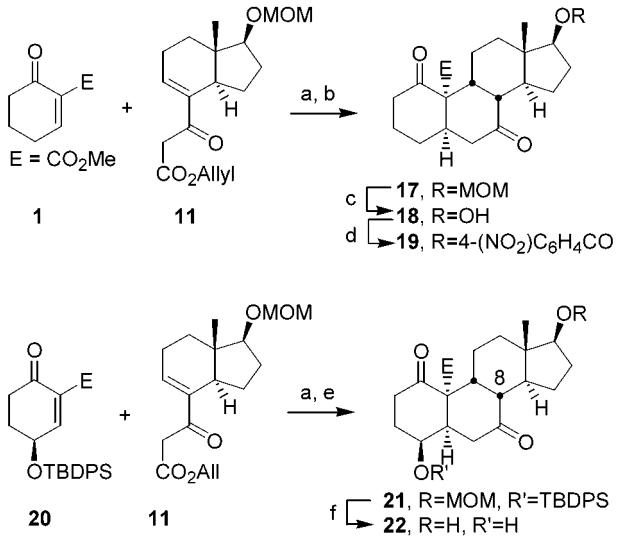
(14) The authors wish to thank Mr. M. Drouin for X-ray diffraction analysis.

Scheme 4[a]



[a] Reagents and conditions: (a) Cs_2CO_3, CH_2Cl_2, rt; (b) $Pd(PPh_3)_4$, morpholine, THF, rt, 87% (two steps); (c) HCl concentrated, MeOH, reflux, 85%; (d) 4-nitrobenzoyl chloride, pyridine, DMAP, CH_2Cl_2, rt, 80%; (e) $Pd(PPh_3)_4$, morpholine, THF, rt, 50% (two steps); (f) HF·pyridine, THF, 80 °C, 78%.

cyclohexenone and could favor the β face of the Nazarov reagent for the cycloaddition.[15,16] The cycloaddition was carried out, and after selective decarboxylation, a new tetracycle, compound **21**, was produced showing that again the angular methyl group on Nazarov reagent **11** controlled the face of the attack (Figure 1, approach **D** was favored over **C**). A slight amount of epimeric tetracycle (approximately 8:1) at position 8 was also observed during the reaction. The alcohols on **21** were deprotected, the resulting tetracyclic compound **22** was crystallized, and its structure was confirmed by X-ray diffraction analysis.[14]

The cycloaddition of *cis* Nazarov reagent **15** was then studied (Scheme 5). Its reaction with cyclohexenone **1** gave

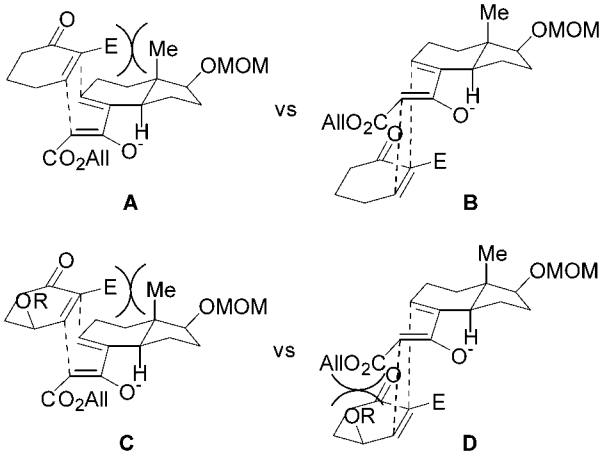
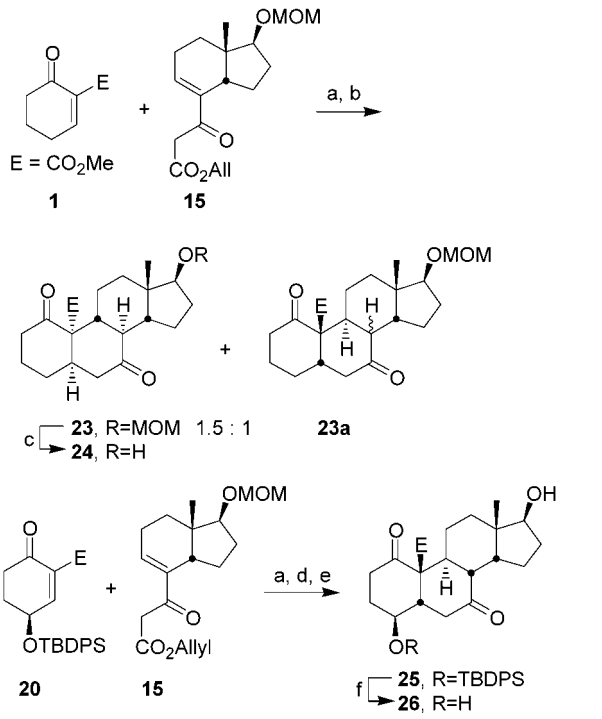


Figure 1. Comparison of the cycloaddition approaches of **1** and **11** (**A**, **B**) and of **20** and **11** (**C**, **D**).

Scheme 5[a]



[a] Reagents and conditions: (a) Cs_2CO_3, CH_2Cl_2, rt.; (b) $Pd(PPh_3)_4$, morpholine, THF, rt, 24% (two steps); (c) HCl concentrated, MeOH, reflux, 85%; (d) $Pd(PPh_3)_4$, morpholine, THF, rt 60% (two steps); (e) HCl concentrated, MeOH, reflux, 99%; (f) aqueous HF, CH_3CN, 75 °C, 75%.

a separable mixture of two tetracyclic compounds **23** and **23a** (unknown configuration at C-8) with low yields and selectivities. The yield can be explained by the low reactivity of Nazarov reagent **15** and the instability of cyclohexenone **1**. On the other hand, the lack of selectivity can be explained by the similarity of steric interactions on the two faces of reagent **15**. After deprotection of the alcohol, an X-ray diffraction analysis[14] of compound **24** proved the structure of the major product.

To obtain better selectivity in the reaction, the cycloaddition was tried with the more stable cyclohexenone **20**. This reaction gave a 1:1 mixture of epimeric compounds at position 8 that under acidic conditions was converted completely into the thermodynamically more stable compound **25**. This result shows that steric interactions produced by the protected alcohol blocking the β face of the cyclohexenone were able to control the cycloaddition's selectivity (Figure 2, approach **A** was favored over **B**). X-ray diffraction analysis[14] of compound **26** proved the structure of **25**.

In conclusion, we have demonstrated that it is possible to perform a double Michael cycloaddition using a bicyclic Nazarov reagent. We also have shown that the tertiary methyl group on the Nazarov reagent controls the selectivity of the

(15) The cycloaddition of cyclohexenone **20** with Nazarov reagent **2** produced 5 β-H, 9 β-Me, and 10 β-E decalin with high yield and stereoselectivity.

(16) Belzile, J.; Chapdelaine, D.; Deslongchamps, P. Unpublished results.

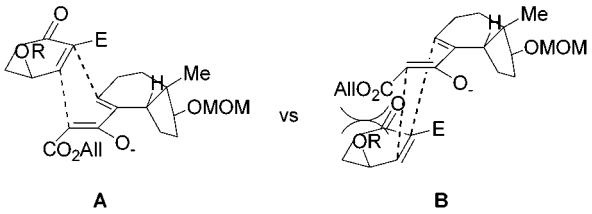


Figure 2. Comparison of the cycloaddition approaches of **20** and **15**.

cycloaddition when the reagent ring junction is *trans* (**11**) by blocking its β face. The use of a chiral 4-substituted-2-carbomethoxy-2-cyclohexenone controls the selectivity when the reaction was carried out with the Nazarov reagent bearing a *cis* ring junction (**15**). This methodology allowed us to obtain in a convergent manner tetracyclic compounds and seems promising for the total synthesis of steroidal natural products. Further developments on this approach with other bicyclic Nazarov reagents are presently being pursued in our laboratories and will be reported in due course.

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Supporting Information Available: Experimental details and characterization data for all compounds and X-ray crystal structure data for compounds **19**, **22**, **24**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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