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Versatile Strategy to Access Tricycles Related to Quassinoids and Triterpenes

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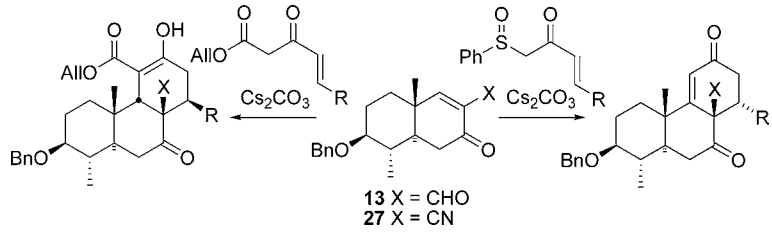
ABSTRACT

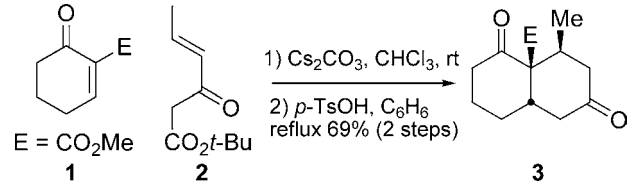


The reactivity of two new bicyclic cyclohexenones (13 and 27) with several Nazarov reagents is presented. A flexible synthetic strategy is developed and provides access to highly substituted tricycles related to quassinoids and triterpenes.

The stereocontrolled reaction of a cyclohexenone **1** and a Nazarov reagent **2**,[1] known as anionic polycyclization, has been a major topic of interest in our laboratory for several years (Scheme 1). The reaction consists of two successive Michael additions and is analogous to a cycloaddition such as the Diels−Alder reaction.[2]

Since its discovery in 1988,[3] this synthetic tool was used to provide a one-step construction of a racemic 13-α-methyl 14-α-hydroxy steroid,[4] an optically active 13-*β*-methyl 14-*β*-hydroxy steroid,[5] a convergent and expedient synthesis of steroids using bicyclic Nazarov reagents,[6] a convergent route to access various tricyclic and tetracyclic products related to sterols,[7] and a novel synthesis of highly functionalized 14-*β*-hydroxysteroids related to Batrachotoxin.[8] This methodology finally proved once again its value in the first total

Scheme 1



synthesis of Ouabain,[9] a cardioactive glycoside isolated from the bark of the African ouabio tree (*Acokanthera ouabio*).[10]

In the array of possible natural product targets, quassinoids caught our attention. Quassinoids are a group of terpenoid natural products mainly isolated from *Simaroubaceae* species,[11] the most well-known members of the family being quassin and bruceantin (Figure 1). The highly oxygenated pentacyclic framework of bruceantin, coupled with its

(1) Nazarov, I. N.; Zauyalou, S. I. *Zh. Obshch. Khim.* **1953**, *23*, 1703.
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(3) Lavallée, J.-F.; Deslongchamps, P. *Tetrahedron Lett.* **1988**, *29*, 5117.
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(10) (a) Arnaud, A. C.R. *Hebd. Seances Acad. Sci.* **1888**, *106*, 1011. (b) Arnaud, A. C.R. *Hebd. Seances Acad. Sci.* **1888**, *107*, 1062. (c) Fieser, L. F.; Fieser, M. *Steroids*; Reinhold: New York 1959:Chapter 20.
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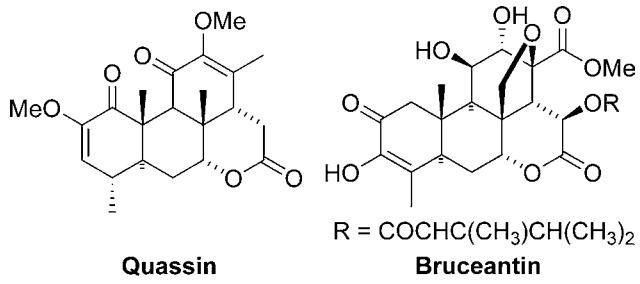


Figure 1. Examples of quassinoids.

complex stereochemical configuration, makes it an attractive target in organic synthesis. Since its isolation in 1973,[12] several groups came up with synthetic strategies for the preparation of highly functionalized intermediates.[13] A formal synthesis (relay) has been reported by Takahashi in 1990[14] and was followed by the first total synthesis in 1993 by the group of Grieco.[15]

In our group, previous polycyclization strategies only involved a monocyclic cyclohexenone structurally similar to **1** in the double Michael addition key step. Acyclic and bicyclic Nazarov reagents, on the other hand, have been used with great success.[6] We now wish to report the reactivity of two new bicyclic cyclohexenones with Nazarov reagents and their application in a natural product synthetic strategy.

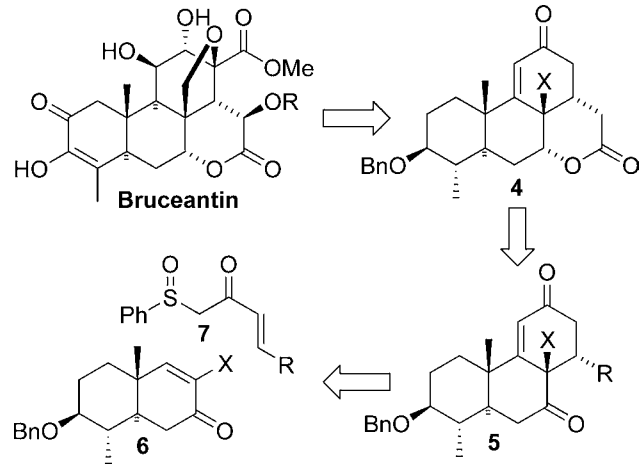
By inspecting the bruceantin stereochemical framework and based on our double Michael reaction methodology, a retrosynthetic analysis would lead to the lactone intermediate **4** (Scheme 2). Prior to lactonization, cycloadduct **5** would be the result of a double Michael addition between bicyclic cyclohexenone **6** (X = CHO, CN) and appropriately substituted Nazarov reagent **7**.

The synthesis of bicyclic cyclohexenone **13** is depicted in Scheme 3. The synthesis started with lactol **8** (obtained by the Robinson annulation of (−)-dihydrocarvone with ethyl vinyl ketone)[16] which was dehydrated with KOH in MeOH.[16] The resulting enone was carefully[17] reduced to the equatorial alcohol under Birch conditions.[18] The secondary alcohol was then protected with a benzyl group to afford coumpound **9**.

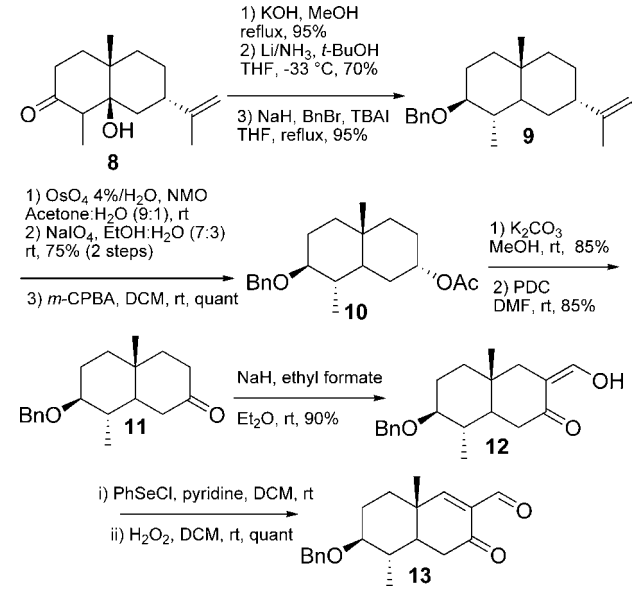
Having served its diastereomeric control purpose in the annulation reaction, the isopropenyl group was then dihydroxylated by the catalytic action of osmium tetroxide. The diol was cleaved to the ketone which was then treated with an excess of *m*-CPBA to afford the corresponding acetate **10** upon Baeyer−Villiger oxidation. Hydrolysis and PDC oxidation afforded ketone **11** which was reacted with sodium hydride and ethyl formate to give rise to β-keto-aldehyde **12**. The insaturation was installed by reacting **12** with phenyl selenium chloride and pyridine, followed by an oxidative quench to provide the expected cyclohexenone **13**, used directly for the double Michael addition.[19]

The next step in our synthesis was to prepare suitably substituted Nazarov reagents (Scheme 4). Monoprotection of propanediol followed by Swern oxidation and Wittig

Scheme 2



Scheme 3



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(14) Sasaki, M.; Murae, T.; Takahashi, T. *J. Org. Chem.* **1990**, *55*, 528.

(15) VanderRoest, J. M.; Grieco, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 5841.

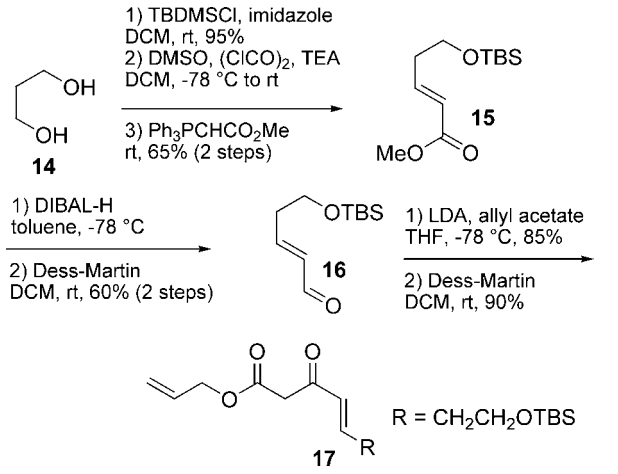
(16) Macias, F. A.; Aguilar, J. M.; Molinillo, J. M. G.; Rodriguez-Luis, F.; Collado, I. G.; Massanet, G. M.; Fronczek, F. R. *Tetrahedron* **2000**, *56*, 3409.

(17) Sequential reduction was necessary to prevent isopropenyl group reduction.

(18) Hua, D. H.; Venkataraman, S. *J. Org. Chem.* **1988**, *53*, 1095.

(19) Liotta, D.; Barnum, C.; Puleo, R.; Zima, G.; Bayer, C.; Kezar III, H. S. *J. Org. Chem.* **1981**, *46*, 2920. Cyclohexenone **13** was unstable and was prepared freshly prior to use, without any purification.

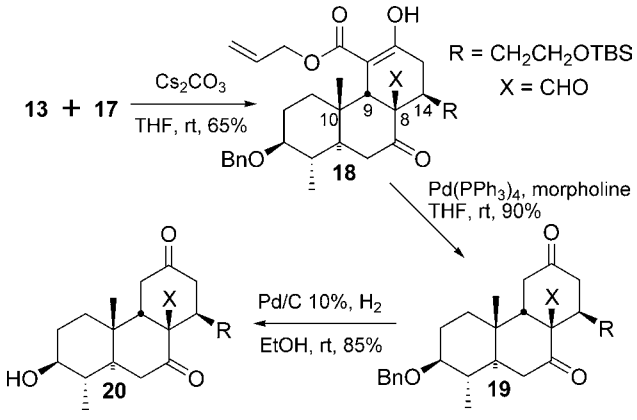
Scheme 4



reaction afforded ester **15**. DIBAL-H reduction, addition of the allyl acetate anion produced by LDA, and Dess-Martin oxidation of the resulting alcohol gave Nazarov reagent **17**. We then explored the reaction of our bicyclic cyclohexenone **13** with β-keto-ester Nazarov reagent **17**.

Reaction of cyclohexenone **13** and Nazarov reagent **17** (R = CH_2CH_2OTBS) with cesium carbonate in THF gave the corresponding diastereomer **18** exclusively in a fair yield of 65% (Scheme 5). The stereochemistry at C9 (steroid

Scheme 5

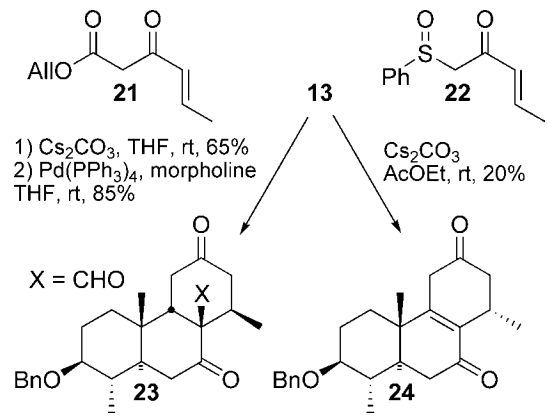


numbering) is directly influenced by the angular methyl group at C10 (1,2-induction). This angular methyl group forces the Nazarov reagent to attack on the α face of the cyclohexenone ring, sterically directing the stereochemical outcome (C9 hydrogen and C8 substituent *cis* to C10 methyl).

Stereochemistry at C14 results from the exclusive *exo* approach of the Nazarov reagent. Further decarboxylation and removal of the benzyl group provided tricycle **20**. Due to the lack of crystallinity of compounds **18**, **19**, and **20**, we next looked at reducing the size of the Nazarov R group to assign C14 stereochemistry.

On the basis of previous results,[20] it is known that a β-keto-sulfoxide Nazarov reagent can reverse the C14 stereochemistry. With both Nazarov reagents **21** and **22**[20] in hand, cyclization with cyclohexenone **13** was undertaken (Scheme 6).

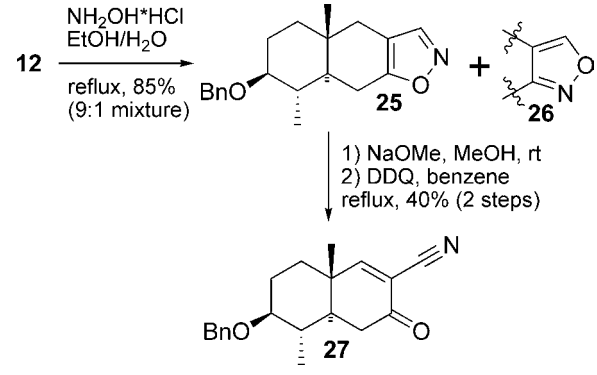
Scheme 6



Cyclization of Nazarov reagent **21** proceeded with the same ease, and the corresponding tricycle was obtained in 65% yield. Upon decarboxylation, tricycle **23** delivered crystalline material which could be analyzed by single-crystal X-ray diffraction analysis to assign C14 stereochemistry to be the one represented (and expected). On the other hand, β-keto-sulfoxide Nazarov **22** gave product **24** coming from deformylation of the aldehyde group upon cyclization. Stereochemistry was later confirmed based on other results. Investigation of a new electron-withdrawing group was our next concern.

Having β-keto-aldehyde **12** in hand, the access to a β-keto-cyano enone was straightforward (Scheme 7). Condensation

Scheme 7



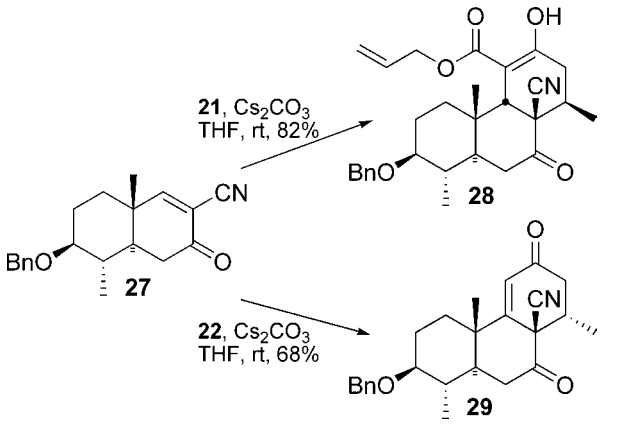
of **12** with hydroxylamine HCl salt gave a 9:1 mixture of isoxazole isomers **25** and **26**.[21] The major isomer was then

(20) Spino, C.; Deslongchamps, P. *Tetrahedron Lett.* **1990**, *31*, 3969.

opened to the α-cyano ketone before completing the formation of the conjugated system by refluxing with DDQ in benzene.[21] The reactivity of this new bicyclic cyclohexenone **27** was then studied with Nazarov reagents **21** and **22**.

The double Michael addition between enone **27** and Nazarov reagent **21** afforded the corresponding cycloadduct **28** in an excellent 82% yield (Scheme 8). Stereochemistry

Scheme 8



was assigned based on previous results obtained with enone **13**. Moreover, β-keto-sulfoxide reagent **22** reacted with enone **27** to give cycloadduct **29** in 68% yield. Upon cyclization, the sulfoxide group suffered a Cope elimination to provide the corresponding enone. Fortunately, this newly formed tricycle crystallized readily, and the stereochemistry was assigned by single-crystal X-ray diffraction analysis. The C14 stereochemistry resulted from an exclusive *endo* approach of Nazarov reagent **22**.

With compounds **28** and **29** in hand, we have obtained highly functionalized tricycles bearing many synthetic levers to push forward quassinoids or triterpenes total synthesis. In one double Michael cyclization step, the formation of a new cycle is accompanied by the control over the formation of three contiguous stereocenters. The cyclohexenone angular methyl group (C10) directs the formation of stereocenters 8 and 9. C14 stereochemistry is determined by the approach of the Nazarov reagent, modulated by the Nazarov β group (ester versus sulfoxide, *exo* versus *endo*). Tricycle **29** possesses the right stereochemical pattern for quassinoids, and tricycles **18** and **28** are well suited for the synthesis of pentacyclic triterpenes or steroids analogues.

We have demonstrated the reactivity of two new bicyclic cyclohexenones **13** and **27** with three Nazarov reagents. Highly functionalized cycloadducts have been obtained and, with proper substitutions, are appropriate for the total synthesis of many natural products (quassinoid, triterpene, steroid). Further developments on this approach and studies toward total synthesis are now being pursued in our laboratory and will be reported in due course.

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Supporting Information Available: Experimental section, physical and spectral data for all new compounds, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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