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Stereoselective Synthesis of Spirocyclic Ketones by Nazarov Reaction

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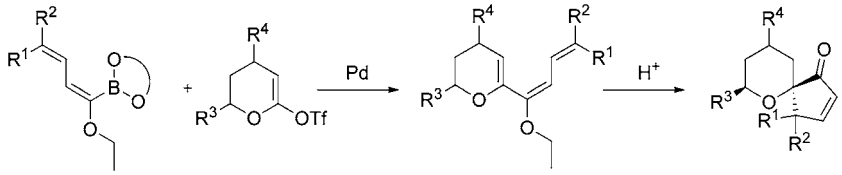
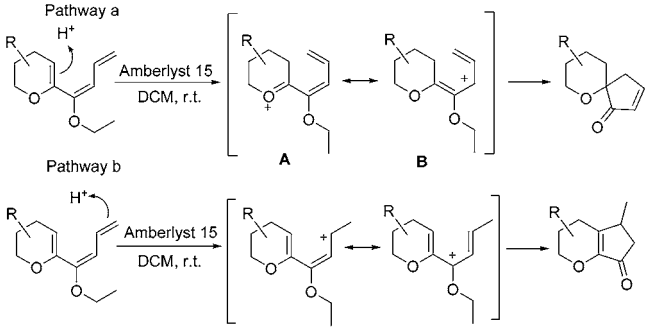
ABSTRACT



The Suzuki–Miyaura cross-coupling reaction between α-ethoxydienyl boronates and lactone-derived vinyl triflates affords functionalized 6-(1-ethoxy-1,3-butadienyl)dihydropyran derivatives that undergo a Nazarov electrocyclic reaction under mild acidic conditions to give functionalized spirocyclic ketones. The product distribution and the stereoselectivity of the process are strongly dependent on the substitution of both the α-ethoxydiene and dihydropyran moieties. High stereoselectivity is observed in the presence of a C2-substituent on the dihydropyran moiety. The results are explained in terms of transition state geometries.

In the course of our investigation on the Nazarov reaction[1] of 6-(1-ethoxy-1,3-butadienyl)dihydropyran derivatives, a work that was aimed at the synthesis of cyclopenta-fused heterocycles,[2] we came across an unexpected, concurrent Nazarov process that formed spirocyclic ketones as secondary products (Scheme 1, pathway a).[3] The relative amount of the spiro byproducts seemed dependent on the ring substitution, in particular, variable amounts (10−24%) of spirocyclic ketones were obtained with 2- and 4-substituted dihydropyran derivatives, whereas unsubstituted dihydropyrans reacted exclusively according to pathway b (Scheme 1). Interestingly, the corresponding *N*-heterocycle derivatives did not give the spirocyclic framework upon treatment with acids but gave solely the target cyclopenta-fused systems.[2,3] These intriguing results prompted us to study in more detail the acid-catalyzed spirocyclization of 6-(1-ethoxy-1,3-butadienyl)dihydropyran derivatives. This process could in fact be useful for the synthesis of biologically active spirocyclic compounds,[4,5] provided the role of the substituents on the ring and on the

Scheme 1. Possible Nazarov Reaction Pathways



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(1) (a) Nazarov, I. N.; Torgov, I. B.; Terekhova, L. N. *Izv. Akad. Nauk. SSSR Otd. Khim. Nauk.* **1942**, 200. (b) Braude, E. A.; Forbes, W. F. *J. Chem. Soc.* **1953**, 2208−2216. (c) Habermas, K. L.; Denmark, S. E.; Jones, T. D. *Org. React.* **1994**, *45*, 1−158. (d) Denmark, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 751−784. (e) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479−6517.

(2) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Venturello, P. *J. Org. Chem.* **2003**, *68*, 9728−9741.

(3) Prandi, C.; Ferrali, A.; Guarna, A.; Venturello, P.; Occhiato, E. G. *J. Org. Chem.* **2004**, *69*, 7705−7709.

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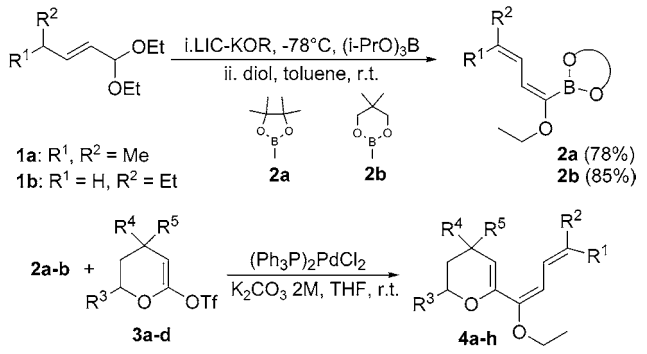
diene in determining the reaction pathway could be understood (Scheme 1, pathways a or b). To the same end, we also evaluated the influence of the heterocycle substituents on the stereoselectivity of the spirocyclization process. On the basis of our previous studies on the torquoselectivity of the Nazarov reaction,[3] we opted to undertake a comparison of the diastereoselectivity exhibited by 2- and 4-substituted dihydropyran derivatives.

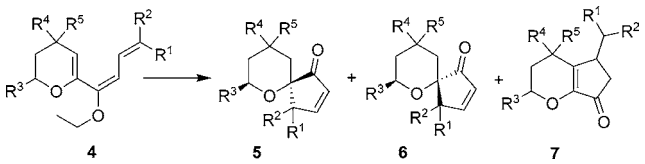
To evaluate the role of the substituents on the dienyl moiety we prepared dienylboronates **2a,b** mono- and disubstituded at C4 (Scheme 2). Boronate **2a** (R^1, R^2 = Me) was synthesized starting from the diethyl acetal of 4-methyl-2-pentenal, in the presence of 4 equiv of LIC−KOR (LIC = butyllithium and KOR = potassium *tert*-butoxide),[6] an excess of base being required to abstract a methinic proton. The boronate was isolated as the pinacol ester, which proved more stable than the corresponding 2,2-dimethylpropandiol derivative.[7] Vinyl triflates **3a**−**d** were obtained by treating the corresponding lactones with KHMDS and $PhNTf_2$ as previously described.[3] Trienes **4e**−**h** were finally obtained in good yields (53−81%) by Pd-catalyzed coupling reaction between **3a**−**d** and boronates **2a,b** (Scheme 2). Trienes **4a**−**d** (R^1, R^2 = H) have already been synthesized.[2,3]

Scheme 2. Synthesis of 6-(1-Ethoxy-1,3-butadienyl)dihydropyrans



Standard conditions to perform the Nazarov reactions were achieved by using Amberlyst 15 in commercial anhydrous DCM under argon or nitrogen atmosphere. The results obtained are summarized in Table 1. When trienes **4a**−**d**, unsubstituted on the ethoxydienyl fragment, were subjected to mild acidic treatment, cyclopenta-fused ketones **7a**−**d** were the main products (Table 1, entries 1−4), with only small amounts (10−24%) of the spiro compound. Only **5b** was obtained as a single diastereomer, whereas a mixture of **5c** and **6c** and a mixture of **5d** and **6d** were isolated.

Table 1. Nazarov Cyclization of Ethoxytrienes **4a**−**h**



entry	4	R^1	R^2	R^3	R^4	R^5	**5**: **6**: **7**[a] (ratio)	yield (%)
1	**a**	H	H	H	H	H	0:0:100	62[c]
2	**b**	H	H	Me	H	H	10:0:90	85[d]
3	**c**	H	H	H	Me	H	24[b]:76	88[d]
4	**d**	H	H	H	Me	Me	10[b]:90	69[d]
5	**e**	Me	Me	H	H	H	100:0:0	72[c]
6	**f**	Me	Me	H	Me	H	50:50:0	74[d]
7	**g**	Me	Me	Me	H	H	100:0:0	58[c]
8	**h**	H	Et	Me	H	H	75:0:25	66[e]

[a] Ratio determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Mixture of diastereoisomers **5** and **6**. [c] Isolated yields after flash chromatography. [d] Combined isolated yields after flash chromatography. [e] Yield of pure **5h**.

When trienes **4e**−**g**, in which the dienyl moiety is *gem*-dimethyl-substituted, were treated with Amberlyst 15, the spiro-ketones were the only products recovered (Table 1, entries 5−7) as diastereopure compounds (**5g**, Table 1, entry 7) or as a 1:1 mixture of diastereomers (**5f** and **6f**, Table 1, entry 6). A mixture of diastereopure spiro-adduct **5h** (75%) and fused-bicyclo system **7h** (25%) was finally obtained with monosubstituted diene **4h** (Table 1, entry 8).

Spiro compounds **5e**, **5g**, **5h**, and **5f** + **6f** were isolated and fully characterized. Spirocyclic ketones from **4b**−**d** were not isolated as pure compounds. However, in the case of **5b**, we managed to assign the stereochemistry on the basis of NMR studies of a chromatographic fraction enriched in the spiro compound. Spiroketones derived from the reaction of 2-methyl-substituted **4b**, **4g**, and **4h** were all obtained as pure diastereoisomers (**5b**, **5g**, and **5h)** in which the new C4−C5 bond is axially oriented and *trans* to the equatorial methyl group at C7. This configuration has been assigned on the basis of 1D and 2D NMR NOESY experiments (Figure 1). For **5b,** the cross-peak between H7 (at 3.6 ppm) and the methylene protons of the cyclopentenone that resonate as a narrow multiplet at about 2.8 ppm is diagnostic.

Only a diaxial relative orientation of the C-H7 and the newly formed C5−CH_2 bond could account for this NOE enhancement, the calculated distance between the closest involved protons being ∼2.25 Å (this distance is >4 Å in the diequatorial conformation, i.e., too high for observing a NOE effect).[8] In the case of **5g** the configuration has been unequivocally assigned by X-ray analysis.[9] The ROESY spectrum shows two cross-peaks between H7 and the geminal

(4) For example, spirocyclic bis-*C*,*C*-glycosides have been synthesized from spirocyclic ketones obtained by the pinacol rearrangement of dihydropyranyl carbinol. Paquette, L. A.; Lanter, J. C.; Johnston, J. N. *J. Org. Chem.* **1997**, *62*, 1702−1712.

(5) Spirocyclization through the Nazarov reaction of divinyl ketones has been exploited for the synthesis of natural compounds. (a) Kraft, P.; Cadalbert, R. *Synthesis* **2002**, *15*, 2243−2253. (b) Kuroda, C.; Hirono, Y. *Tetrahedron Lett.* **1994**, *35*, 6895−6896.

(6) (a) Schlosser, M. *J. Organomet. Chem.* **1967**, *8*, 9−16. (b) Schlosser M. *Mod. Synth. Methods* **1992**, *6*, 227−271. (c) Mordini, A. In *Advances in Carbanion Chemistry*; Snieckus, V., Ed.; JAI Press: Greenwich, CT, 1992; Vol. 1, pp 1−45. (d) Schlosser, M.; Faigl, F.; Franzini, L.; Geneste, H.; Katsoulos, G.; Zhong, G. *Pure Appl. Chem.* **1994**, *66*, 1439−1446. (e) Lochmann, L. *Eur. J. Inorg. Chem.* **2000**, 1115−1126.

(7) Balma Tivola, P.; Deagostino, A.; Prandi, C.; Venturello, P. *Org. Lett.* **2002**, *4*, 1275−1277.

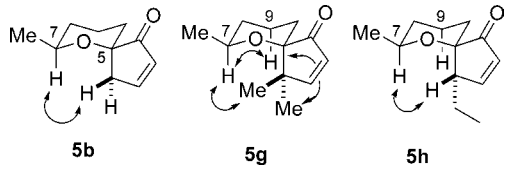


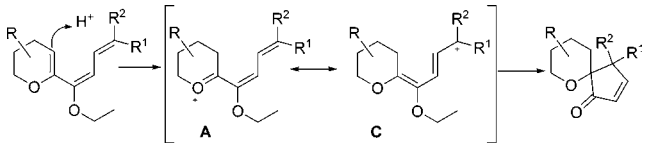
Figure 1. Observed NOE enhancements in compounds **5b**, **5g**, and **5h**.

methyl groups on the cyclopentenone (distances of 2.173 and 2.780 Å by X-ray). Also, other cross-peaks are found between an (axial) proton on C9 and H7, as well as the same proton on C9 and only one of the two geminal methyl groups (distance 2.163 Å, X-ray). These data are accounted for only by assuming, again, that C-H7 and the newly formed C5−CMe_2 bonds are diaxial. Finally, in the case of **5h**, there is the further problem of assigning the relative stereochemistry of the new stereocenter on the cyclopentenone. The diaxal relative orientation of C-H7 and the newly formed C5−CHEt explains the strong NOE observed between H7 and the proton on the cyclopentenone stereocenter ($d \sim 2.2$ Å). A very weak NOE between H7 and one of the proximal protons of the ethyl group ($d > 3$ Å) is consistent with the *endo* orientation of the ethyl group.

In Scheme 1 are shown the two different pathways that lead to spirocyclic compounds (pathway a) and to cyclopenta-fused heterocycles (pathway b); pathway b being always predominant with unsubstituted ethoxydiene **4a**−**d**. The formation of the spiro compounds could be explained by admitting the initial protonation of the endocyclic double bond with the formation of a pentadienyl cation possessing the electronic arrangement to give a Nazarov reaction.

It is reasonable to suppose that pathway a could be favored by the stabilization of the positive charge by the heteroatom in resonance structure **A** (Scheme 3 and Scheme 1).

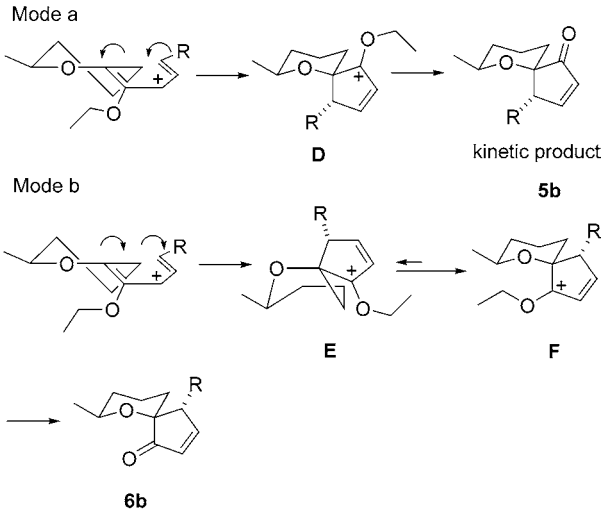
Scheme 3. Effect of Distal Substituents on Cyclization



Moreover, the presence of one or two subsituents on the distal C atom of the diene moiety makes the endocyclic protonation more competitive as a result of the contribution of structure **C** (Scheme 3). The results of the substitution start to be visible in the case of **4h** (R^1 = H, R^2 = Et, 75% spiro compound, 25% cyclopenta-fused compound) where a secondary carbocation is formed. The effect is largest in the case of **4g** where the endocyclic protonation generates a tertiary carbocation. In this case pathway a (Scheme 1) becomes predominant and the spiro compound is the only possible product. [110]

The conrotatory spirocyclization results in the generation of a new stereogenic center at C5. Reasonably, the electrocyclization process is triggered by the initial protonation of the endocyclic double bond with generation of the requisite pentadienyl cation **B** (Scheme 1). In case of substituted dihydropyran derivatives such as **4b** two rapidly equilibrating semi-chair conformations are possible, one of them being thermodynamically less stable because of the axial position of methyl on C2. We can therefore assume that the conformer in which the methyl group is equatorially oriented is involved in the electrocyclization.[10] The two possible conrotation modes, clockwise and counterclockwise (Scheme 4), lead

Scheme 4. Conrotation Modes in Spirocyclization



to the two different diastereomers. The counterclockwise conrotation (mode a) would imply a chair-like arrangement of the transition structure (structurally close to intermediate **D**), which maintains the methyl group equatorially oriented and delivers kinetic product **5b**. Alternativly, a clockwise conrotation (mode b) proceeds through a less favored twist-boat transition structure (close to intermediate **E**). Intermediate **E** could then equilibrate with a less energetic intermediate **F** to furnish thermodynamically more stable product **6b** (molecular mechanics calculations resulted in diastereomer **6b** being more stable than **5b** by 2.3 kcal·mol^{-1}).[8] The preferred chair-like conformation of the transition structure involved in mode a, in which the methyl group is equatorial,

(8) Molecular modeling calculations were performed by using the MM2* force field implemented in MacroModel. Mohamadi, F.; Richards, N. G.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem* **1990**, *11*, 440−467. Chloroform was set as the solvent in the calculations.

(9) Crystallographic data for compound **5g** have been deposited at the Cambridge Crystallographic Data Centre (deposition no. CCDC 274489). ORTEP view and CIF file for compound **5g** have been also reported as Supporting Information.

(10) Consistently, *gem*-disubstituted pyrrole derivatives do not hydrolize to divinyl ketons and are recovered unreacted after treatment with acid. Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A. *J. Org. Chem.* **2005**, *70*, 4542−4545.

could explain the high diastereoselectivity observed in the formation of the diastereoisomer **5b**.

The same considerations apply to the highly diastereoselective spirocyclization of 2-methyl-substituted compounds **4g** and **4h**. In the latter case the *endo* orientation of the ethyl group in **5h** is consistent with the counterclockwise mode a. The lack of diastereoselectivity for 4-substituted derivatives (Table 1, entries 3, 4, and 6) is less clear. It is known that in 2-substituted systems oxygen heterocycles display a larger $-\Delta G°$ for the two chair conformations having a methyl axial and equatorial than does cyclohexane. This is probably due to the shorter length of the C−O bond with respect to a C−C bond. As a consequence, the distance between an axial methyl at C2 and an axial group at C6 involves a considerable enhanced steric strain. On the contrary, methyl groups at C4 are conformationally "cyclohexane-like". The result of this major conformational freedom is that both conformations of the cation B (Scheme 1), with the C4 methyl axial or equatorial, could be involved in the formation of the new bond. Chair-like arrangements of the likewise stabilized TS afford a mixture of diastereoisomers.[12]

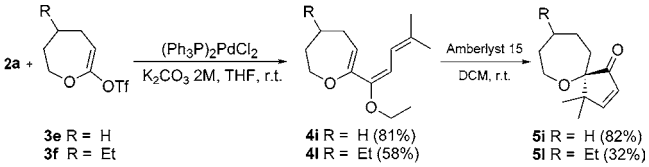
The same synthetic approach was finally applied to seven-membered oxacycles, to obtain spirooxepanes. Trienes **4i** and **4l** (Scheme 5) were obtained by the usual Suzuki−Miyaura cross-coupling reaction and purified by flash chromatography. Acidic treatment with Amberlyst 15 affords the spiro-products **5i**−**l**. As a consequence of the conformational flexibility of the seven-membered rings, a lack in diastereoselection would be expected in the cyclization of **4l**.

In fact, GC, GC−MS, and ^{1}H NMR analysis of the crude reaction mixtures showed the presence of two diastereoisomers in a 3/1 ratio. Flash chromatography was accomplished with a high degree of product decomposition, so that only one diastereoisomer was recovered.

(11) The same assumption has been made by Paquette for the oxonium ion initiated pinacol rearrangement of dihydropyranyl carbinol. Paquette, L. A.; Lanter, J. C.; Johnston, J. N. *J. Org. Chem*. **1997**, *62*, 1702−1712.

(12) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994.

Scheme 5. Synthesis of Spirooxepanes



In conclusion, with this work we have demonstrated that it is possible to modulate the course of the acid-catalyzed cyclization of 6-(1-ethoxy-1,3-butadienyl)dihydropyran derivatives in order to selectively obtain spirocyclic ketones. One or two alkyl substituents on the distal sp^2 carbon atom of the ethoxydiene moiety are in fact sufficient to move the process toward the spirocyclization. Diastereopure compounds are then obtained in the case of 2-alkyl-substituted dihydropyran rings, therefore making the procedure potentially useful for the synthesis of spirocyclic bis-*C*,*C*-glycosides.

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Supporting Information Available: Full experimental details and spectroscopic characterization for the new compounds prepared, and ORTEP views (Figures S1 and S2) and CIF file for compound **5g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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