

New Synthetic Approach to Cyclopenta-Fused Heterocycles Based upon a Mild Nazarov Reaction. 2. Further Studies on the Torquoselectivity

Cristina Prandi,^{*,†} Alessandro Ferrali,[‡] Antonio Guarna,[‡] Paolo Venturello,[§] and Ernesto G. Occhiato^{*,‡}

Dipartimento di Scienze dell'Ambiente e della Vita, Università del Piemonte Orientale, Spalto Marengo 33, 15100 Alessandria, Italy, Dipartimento di Chimica Organica "U. Schiff", Università di Firenze, Via della Lastruccia 13, I-50019 Sesto Fiorentino, Italy, and Dipartimento di Chimica Generale ed Organica Applicata, Università di Torino, Corso Massimo D'Azeglio, 48, I-10125 Torino, Italy

cristina.prandi@unito.it; ernesto.occhiato@unifi.it

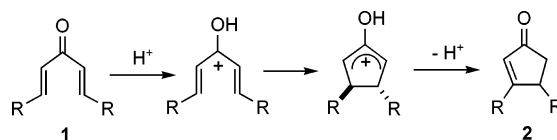
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Conjugated alkoxytrienes in which one of the double bonds is embedded in a heterocyclic moiety are obtained by the Pd-catalyzed coupling reaction of lactam- and lactone-derived vinyl triflates with α -alkoxydienylboronates. These compounds undergo a 4π electrocyclization process (Nazarov reaction) under acidic conditions and afford cyclopenta-fused heterocycles in good yields. As a continuation of a previous study, the torquoselectivity of this Nazarov reaction has been investigated using 2-alkyl-substituted pyrrolidinone and 2- and 4-substituted δ -valerolactone derivatives. High or complete stereoselectivity has only been observed with the 2-alkyl-substituted heterocycles. Both steric and stereoelectronic effects could contribute to determining the stereoselection of the ring closure.

Introduction

Since the initial discovery that divinyl ketones **1** (Scheme 1) undergo a 4π electrocyclization under strong acidic conditions to form 2-cyclopentenones **2** (the Nazarov reaction),^{1,2} steady progress has been made in expanding the synthetic value of this reaction, primarily by the use of Lewis acids as cyclization initiators³ and by procedures called "directed Nazarov cyclization"⁴ and "interrupted Nazarov reaction".⁵ The recently reported palladium(II)-catalyzed Nazarov reaction,⁶ and the first catalytic asymmetric Nazarov reactions promoted by chiral Lewis acids,⁷ are the latest important achievements.

SCHEME 1



Suitable precursors of the pentadienyl cationic intermediate (Scheme 1) have also been used for carrying out the electrocyclization.^{2a,c,d} We have recently shown that conjugated ethoxytrienes **5** (Scheme 2), obtained by Pd-catalyzed cross-coupling reaction of the corresponding lactam- and lactone-derived vinyl triflates or phosphates **3** with α -ethoxydienylboronates **4**,⁸ undergo cyclization when treated with the acidic Amberlyst 15 resin in CHCl_3

* To whom correspondence should be addressed. (C.P.) Tel: +39-011-6707647. Fax: +39-0131-287416. (E.G.O.) Tel: +39-055-4573480. Fax: +39-055-4573531.

[†] Università del Piemonte Orientale.

[‡] Università di Firenze.

[§] Università di Torino.

(1) (a) Nazarov, I. N.; Torgov, I. B.; Terekhova, L. N. *Izv. Akad. Nauk. SSSR Khim. Nauk.* **1942**, 200. (b) Braude, E. A.; Forbes, W. F. *J. Chem. Soc.* **1953**, 2208–2216.

(2) (a) Habermas, K. L.; Denmark, S. E.; Jones, T. D. *Org. React.* **1994**, 45, 1–158. (b) Denmark, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 751–784. (c) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, 123, 8509–8514 and references therein. (d) Forest, J.; Bee, C.; Cordaro, F.; Tius, M. A. *Org. Lett.* **2003**, 5, 4069–4072 and references therein.

(3) (a) Paquette, L. A.; Fristad, W. E.; Dime, D. S.; Bailey, T. R. *J. Org. Chem.* **1980**, 45, 3017–3028. (b) He, W.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2003**, 125, 14278–14279. (c) Janka, M.; He, W.; Frontier, A. J.; Eisenberg, R. *J. Am. Chem. Soc.* **2004**, 126, 6864–6865. (d) Chiu, P.; Li, S. *Org. Lett.* **2004**, 6, 613–616.

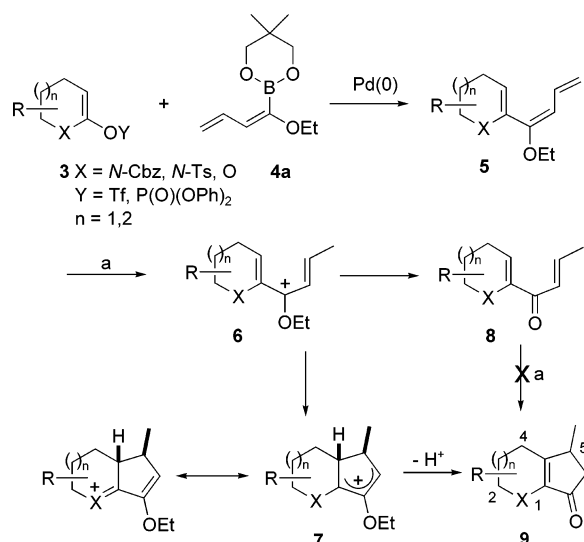
(4) For processes involving β -silyl- or β -stannyl-substituted dienones, see: (a) Denmark, S. E.; Jones, T. K. *J. Am. Chem. Soc.* **1982**, 104, 2642–2645. (b) Jones, T. K.; Denmark, S. E. *Helv. Chim. Acta* **1983**, 66, 2377–2396. (c) Peel, M. R.; Johnson, C. R. *Tetrahedron Lett.* **1986**, 27, 5947–5950. For processes involving fluorine-substituted dienones, see: (d) Ichikawa, J.; Miyazaki, J.; Fujiwara, M.; Minami, T. *J. Org. Chem.* **1995**, 60, 2320–2321. (e) Ichikawa, J.; Fujiwara, M.; Okauchi, T.; Minami, T. *Synlett* **1998**, 927–929.

(5) (a) Giese, S.; West, F. G. *Tetrahedron* **2000**, 56, 10221–10228. (b) Wang, Y.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, 121, 876–877. (c) Bender, J. A.; Blize, A. E.; Browder, C. C.; Giese, S.; West, F. G. *J. Org. Chem.* **1998**, 63, 2430–2431.

(6) Bee, C.; Leclerc, E.; Tius, M. A. *Org. Lett.* **2003**, 5, 4927–4930.

(7) (a) Aggarwal, V. K.; Belfield, A. J. *Org. Lett.* **2003**, 5, 5075–5078. (b) Liang, G.; Gradl, S. N.; Trauner, D. *Org. Lett.* **2003**, 5, 4931–4934. (c) Liang, G.; Trauner, D. *J. Am. Chem. Soc.* **2004**, 126, 9544–9545.

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

SCHEME 2^a

^a Key: (a) Amberlyst 15, CHCl₃, 25 °C.

at room temperature to give the cyclopenta-fused heterocycles **9** in good yields.⁹ For this process, we proposed a Nazarov-type mechanism which includes protonation of the distal double bond and generation of the 3-alkoxy-pentadienylic cation **6**, then electrocyclization to form the oxyallyl intermediate **7**, and eventually, loss of a proton to give **9**. A minor product that is sometimes formed in this process is divinyl ketone **8**, which is not an intermediate in the cyclization process under these mild acidic conditions.^{9b} The stabilization of the positive charge in **7** by the electron-donor atom (nitrogen or oxygen) in the adjacent heterocycle accounts for the mild reaction conditions required.^{9a}

We have also shown that the ring closure is highly diastereoselective in the cases of 2- and 4-alkyl-substituted δ -valerolactam derivatives, which provide 2,5- and 4,5-*cis* disubstituted hexahydro[1]pyrindines **9** (Scheme 2, X = *N*-Cbz, *N*-Ts). In the present work, we report on the torquoselectivity^{2a} in the cyclization of 2-substituted five-membered azacycle and 2- and 4-substituted six-membered oxacycle derivatives. Such a study should provide a more complete picture of the diastereoselection in the Nazarov cyclization of these conjugated ethoxy-trienes, making the whole procedure useful for the construction of cyclopenta-fused heterocycles found in several natural and biologically active compounds, among which are, for example, roseophilin,¹⁰ streptazolin,¹¹ abikoviromycin,¹² pyridicin,¹³ nakadomarin,¹⁴ prostacyclin and its analogues,¹⁵ and serratinin.¹⁶

(9) (a) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Venturello, P. *J. Org. Chem.* **2003**, *68*, 9728–9741. (b) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Deagostino, A.; Venturello, P. *J. Org. Chem.* **2002**, *67*, 7144–7146.

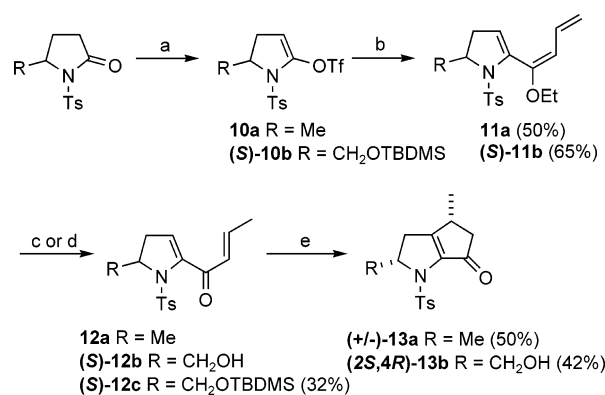
(10) For a review on the chemistry and biology of roseophilin, see: Fürstner A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582–3603.

(11) Nomura, I.; Mukai, C. *J. Org. Chem.* **2004**, *69*, 1803–1812 and references therein.

(12) Maruyama, H.; Okamoto, S.; Kubo, Y.; Tsuji, G.; Fujii, I.; Ebizuka, Y.; Furihata, K.; Hayakawa, Y.; Nagasawa, H.; Sakuda, S. *J. Antibiot.* **2003**, *56*, 801–804.

(13) Omura, S.; Tanaka, H.; Awaya, J.; Narimatsu, Y.; Konda, Y.; Hata T. *Agric. Biol. Chem.* **1977**, *38*, 899–906.

(14) Leclerc, E.; Tius, M. A. *Org. Lett.* **2003**, *5*, 1171–1174 and references therein.

SCHEME 3^a

^a Key: (a) KHMDS, PhNTf₂, THF, –78 °C; (b) **4a**, (Ph₃P)₂PdCl₂ (5%), THF, 2 M Na₂CO₃, 55–60 °C; (c) 0.02 M HCl, MeOH–H₂O 4:1, rt; (d) Amberlyst 15, CHCl₃; (e) neat TFA, rt.

Results and Discussion

To synthesize the azacycles, we coupled vinyl triflates **10a,b** (Scheme 3) with ethoxydienylboronate **4a** in order to obtain the required ethoxytriene derivatives **11a,b**. Commercially available, racemic 5-methyl-pyrrolidin-2-one was converted into the *N*-tosyl derivative,^{9a,17} and this quantitatively transformed into the corresponding triflate **10a** by trapping the enolate with *N*-phenyl triflimide.¹⁸ Since **10a** was rather prone to decomposition on standing, it was promptly coupled with **4a** by using (PPh₃)₂PdCl₂ (5%) as a catalyst in THF, in the presence of aqueous 2 M Na₂CO₃ as a base. The reaction was complete within 3 h at 55 °C and afforded, after chromatographic purification, **11a** in 50% yield (from the *N*-tosyl pyrrolidinone, two steps). In the case of five-membered azacycle derivatives as **11a**, the direct Nazarov cyclization under mild acidic conditions is prevented by the ring strain in the cationic azabicyclo[3.3.0]octenyl intermediate and the corresponding α,β -unsaturated ketone is thus obtained. The latter can be treated with TFA to give the corresponding Nazarov compound.^{9a} The best conditions to obtain **12a** were found by carrying out the hydrolysis with 0.02 M HCl in H₂O–MeOH 1:4 (100% conversion). Subsequent treatment of crude **12a** with neat TFA provided cyclopenta-fused pyrroline **13a** (50% overall yield from **11a**) as a single diastereomer in which the two methyl groups are incorporated in a *cis* relationship. This structural assignment was based on the analysis of a series of NOESY 1D and 2D spectra of **13a**, in which diagnostic cross-peaks between H3 (which resonates at 2.10 ppm) and the two methyl groups on C2 and C4 were present (Figure 1a).

The same synthetic sequence was applied to enantiopure (*S*)-5-hydroxymethylpyrrolidin-2-one. This was suitably O- and N-protected¹⁹ and converted into the corresponding triflate **10b**. Pd-catalyzed coupling with

(15) Johnson, R. A.; Nidy, E. G. *J. Org. Chem.* **1980**, *45*, 3802–3810.

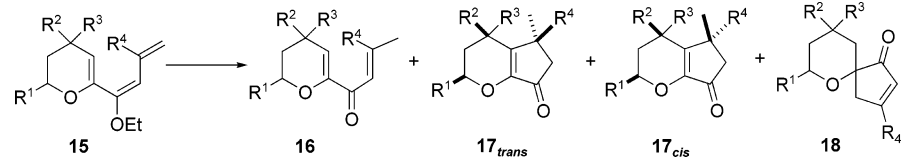
(16) Morita, H.; Kobayashi, J. *J. Org. Chem.* **2002**, *67*, 5378–5381.

(17) Acevedo, C. M.; Kogut, E. F.; Lipton, M. A. *Tetrahedron* **2001**, *57*, 6353–6359.

(18) For a recent review on the chemistry of lactam-derived vinyl triflates, see: Occhiato, E. G. *Mini-Rev. Org. Chem.* **2004**, *1*, 149–162.

(19) Nagashima, H.; Wakamatsu, H.; Ozaki, N.; Ishii, T.; Watanabe, M. *J. Org. Chem.* **1992**, *57*, 1682–1689.

TABLE 2. Hydrolysis Performed on Ethoxytrienes 15



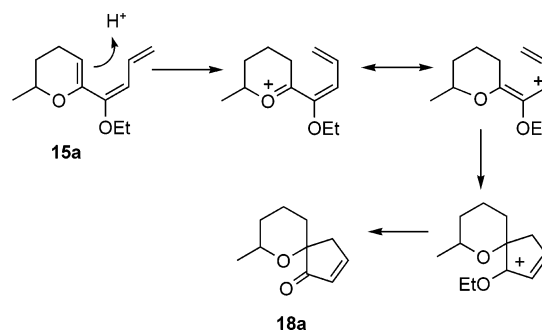
entry	substrate	conditions	<i>T</i> (°C)/time (h)	yield of 16 ^a (%)	yield of 17 + 18 ^b (%)	ratio of 17 _{trans} / 17 _{cis} ^{c,d}	ratio of 17 / 18 ^d
1	15a	Amberlyst 15/DCM	rt/2	<5	85	16:1	90:10
2	15a	0.2 M CF ₃ SO ₃ H in DCM	rt/0.5	n.d. ^e	56	16:1	91:9
3	15b	Amberlyst 15/DCM	rt/4	n.d.	88	1:2	76:24
4	15b	0.2 M CF ₃ SO ₃ H in DCM	rt/0.5	n.d.	85	1:2	94:6
5	15c	Amberlyst 15/DCM	rt/2.5	n.d.	69		90:10
6	15d	Amberlyst 15/DCM	rt/15	45	39	1:3	100:0
7	15e	Amberlyst 15/DCM	rt/1	18	78		100:0
8	15f	Amberlyst 15/DCM	rt/6	57	30		100:0
9	15f	0.2 M CF ₃ SO ₃ H in DCM	rt/0.5	n.d.	67		100:0

^a Yield of open-chain ketone isolated after flash chromatography. ^b Yield of the mixture after flash chromatography. ^c The terms trans and cis refer only to 2,5- and 4,5-disubstituted compounds, i.e., **17a**, **17b**, and **17d**. ^d Ratio determined by integration of proton signals in the ¹H NMR spectrum of the unresolved mixture obtained after flash chromatography and GC analysis. ^e Not detected

In the hydrolysis of 4-methyl-substituted **15b**, the stereochemical control was worse and **17b** ($R^1 = \text{H}$, $R^2 = \text{Me}$, $R^3 = R^4 = \text{H}$) was recovered as a 2:1 mixture of inseparable cis and trans diastereomers (Table 2, entry 3). In this case, the reaction with Amberlyst 15 provided a mixture of Nazarov compound **17b** and spiro compound **18b** in a 3:1 ratio. The relative amount of spiro compound decreased when the reaction was carried out in a 0.2 M CF₃SO₃H solution in DCM (entry 4). Unfortunately, the complexity of the ¹H NMR spectrum of **17b** made any attempt at assigning the stereochemistry to the major diastereomer unfruitful, and we may only assume that it has a cis relative stereochemistry (see below). We thought that an increase of steric hindrance at the C4 would further favor the formation of the spiro compound. However, the hydrolysis of the 4,4-dimethyl-substituted derivative **15c** (entry 5) furnished the same **17/18** ratio as in the case of entry 1. The presence of a phenyl group in position 4 (Table 2, entry 6) made the electrocyclization process more difficult. In this case, dienone **16d** was recovered in 45% yield after chromatography along with **17d** ($R^1 = \text{H}$, $R^2 = \text{Ph}$, $R^3 = R^4 = \text{H}$) as a 3:1 mixture of diastereomers **17d**_{cis} and **17d**_{trans} (39% yield). The formation of the spiro compound **18d** was not observed in this case. In the ¹H NMR spectrum of the 3:1 diastereomeric mixture, the methyl group of the minor component resonates at 1.04 ppm whereas in the major diastereomer it is upfield shifted to 0.83 ppm. This is consistent with the cis relative stereochemistry of the major diastereomer since, as suggested by a molecular modeling study,²³ only through this spatial arrangement can the methyl group undergo the shielding effect of the facing phenyl ring.

Finally, when we subjected trienes **15e,f** ($R^4 = \text{Me}$ in both cases) to hydrolysis (Table 2, entry 7–9), no spiro compounds were detected, but the yields of **16e,f** were enhanced. In these cases, byproducts **16** can be easily transformed into **17** by treatment with neat TFA at room

SCHEME 4



temperature (direct treatment of ethoxydienes **15** with neat TFA affords the Nazarov compounds in poor yield and the reaction is characterized by a large amount of degradation products). In any case, the use of CF₃SO₃H (entry 9) allowed for the complete conversion into the Nazarov product.

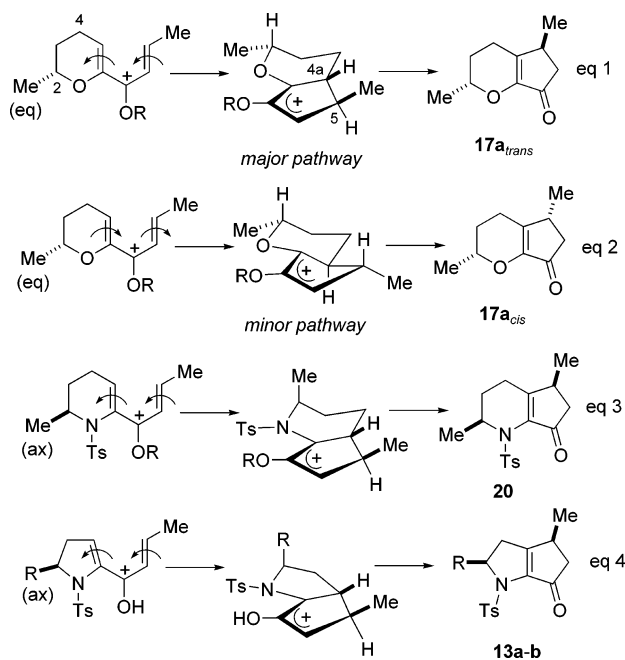
The formation of the spiro byproducts **18** (not found in our previous study on unsubstituted δ -valerolactone derivatives),^{9a} should take place through protonation of the endocyclic double bond favored by the presence of the heteroatom (Scheme 4). This is followed by an alternative Nazarov electrocyclization pathway, the first intermediate in Scheme 4 being just a resonance form of a pentadienyl cation.²⁴ When dienones **16** are treated with TFA they do not give the corresponding spiro compounds. Apart from the detrimental effect of the 3-methyl group in the ethoxydiene moiety of **15e,f** on the formation of the spiro compounds, there is no clear relationship between the structure of ethoxytriene **15** or the reaction conditions and the relative amount of **18** after the hydrolysis. This can be seen from the results presented in Table 2.

We have previously suggested that steric interactions play a part in the selection between the two possible conrotatory pathways in the cyclization of 2- and 4-methyl substituted six-membered lactam derivatives which lead, in both cases, to the exclusive formation of the cis

(23) The MM2* force field was used for the energy minimization with MacroModel software. Mohamadi, F.; Richards, N. G.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. MacroModel—An Integrated Software System for Modeling Organic and Bioorganic Molecules Using Molecular Mechanics. *J. Comput. Chem.* **1990**, *11*, 440–467.

(24) We thank one of the reviewers for the suggestion regarding the possible mechanism of cyclization that leads to the spiro compounds.

diastereomer.^{9a} Instead, in the hydrolysis of 2-methyl substituted lactone derivative **15a** (eq 1), the relative stereochemistry of the major product is trans (**17a_{trans}**). Thus the formation of the new C–C bond must take place on the same side of the 2-methyl group (through a transition structure in which the pyran ring has a boatlike conformation), although nonbonded interactions between this substituent and the incipient C4a–C5 bond should be negligible as the methyl is in a pseudoequatorial position. This should also be true in the case of a clockwise conrotation (eq 2) which would impose a chairlike conformation for the six-membered heterocycle in the transition structure.²⁵ The reasons why the counterclockwise conrotation mode is preferred are unclear. Stereoelectronic effects could play a role: in particular it is possible that there may be a better orbital overlap in the formation of the new C4a–C5 bond when the pyran ring adopts a boatlike conformation in the transition state.



Our previous results obtained with 2-methyl-substituted δ -valerolactam derivatives^{9a} confirm that a boatlike structure for the heterocycle in the transition state is possible. As shown in eq 3, the methyl group is forced to assume an axial orientation because of the N protecting group.²⁶ Consequently, the reaction proceeds via a counterclockwise conrotation involving the less hindered face of the endocyclic double bond through a boatlike transi-

tion structure, which leads to the formation of cis isomer **20** only. As for the 2-alkyl-substituted pyrrolidinone derivatives (eq 4), the substituent is axially oriented and the new bond develops on the opposite site, which provides the cis-substituted compounds **13a** and **13b** with high or total selectivity.

With the 4-substituted lactone derivatives, the formation of the major 4,5-cis isomer **17d_{cis}** in the hydrolysis of 4-phenyl-substituted derivative **15d** is in accordance with Denmark's results in the silicon-directed Nazarov cyclization.²⁷ The attack occurs on the less hindered face of the endocyclic double bond, i.e., opposite the 4-substituent, leading to the cis product. On these grounds it is reasonable to think that **17b_{cis}** is the major diastereomer formed in the hydrolysis of **15b**. In the former case, the higher diastereomeric ratio (3:1) in favor of the cis product could depend on the increased steric demand of the substituent. The low relative amount of Nazarov compound **17d** (39%, Table 2, entry 6) which is formed in the hydrolysis of **15d** (dienone **16d** is obtained in 45% yield), could be due to the enhanced bulk of the 4-substituent. In fact, complete conversion into the dienone has been already observed by us with a lactam derivative when the sterically more demanding 4-*tert*-butyl group was present in the ring.^{9a}

Conclusion. In the present study we provide a complete depiction of the torquoselectivity in the Nazarov reaction of lactam- and lactone-derived ethoxytrienes that furnishes cyclopenta-fused heterocycles. The reaction is highly diastereoselective with 2-substituted five-membered lactam derivatives **11a** and **11b** and leads to cis disubstituted cyclopenta-fused pyrrolines **13a** and **13b**, respectively. This occurs through a conrotation in the 3-hydroxypentadienyl cationic intermediate which involves the less hindered face of the endocyclic double bond. The same is true for 2- and 4-substituted δ -valerolactam derivatives. In contrast, the trans product **17a_{trans}** is predominantly formed with the 2-methyl-substituted δ -valerolactone derivative **15a**, whereas modest selectivity is observed with 4-substituted lactone derivatives **15b** and **15d**. Both steric and stereoelectronic effects could contribute to determining the stereoselection in the ring closure. Ab initio calculations are currently being performed to assess this. The possibility of controlling the stereochemical outcome in such a process makes the methodology potentially useful for the synthesis of natural products and biologically active compounds.

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Supporting Information Available: Experimental procedures and copies of the ¹H NMR spectra of compounds **11a,b**, **13a,b**, **15a–c,e,f**, **17a**, **17a/18a** 1:1 mixture, **17b/18b** 3:1 mixture, and **17c,e** and the ¹³C NMR spectra of the **17a/18a** 1:1 mixture. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(25) In our earlier paper (see ref 9a), we assumed that a transition structure in which the heterocycle had a chairlike conformation could be favored.

(26) (a) Comins, D. L.; Joseph, S. P. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI Press: Greenwich, CT, 1996; Vol. 2, pp 251–294. (b) Kuethe, J. T.; Brooks, C. A.; Comins, D. L. *Org. Lett.* **2003**, 5, 321–323. (c) Ha, J. D.; Kang, C. H.; Belmore, K. A.; Cha, J. K. *J. Org. Chem.* **1998**, 63, 3810–3811. (d) Toyooka, N.; Okumura, M.; Takahata, H.; Nemoto, H. *Tetrahedron* **1999**, 55, 10673–10684. (e) Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, 62, 3592–3596.

(27) Denmark, S. E.; Habermas, K. L.; Hite, G. A.; Jones, T. K. *Tetrahedron* **1986**, 42, 2821–2829.