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New Synthetic Approach to Cyclopenta-Fused Heterocycles Based upon a Mild Nazarov Reaction†

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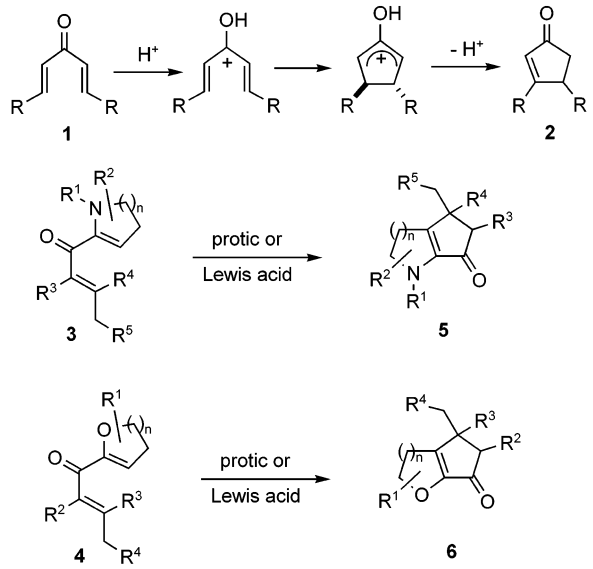
The Pd-catalyzed coupling reaction of lactam or lactone-derived vinyl triflates and phosphates with α-alkoxydienylboronates gives conjugated alkoxytrienes in which one of the double bonds is embedded in a heterocyclic moiety. If subjected to mild acidic hydrolysis, these compounds undergo a 4π electrocyclization process (Nazarov reaction) which furnishes cyclopenta-fused O- and N-heterocycles in good yields. The scope of the work has been that of closely examining the role and effect of both the heteroatom and the heterocycle ring size on the outcome of the electrocyclization, as well as the torquoselectivity of this process. The presence of the heteroatom was essential in stabilizing the oxyallyl cation intermediate, thus allowing the reaction to occur. The ring size was also a basic parameter in the cyclization step: five-membered azacycles required more drastic conditions to give 5−5 fused systems and did so only after an initial hydrolysis to the corresponding divinyl ketones. As for the torquoselectivity, with both 2-methyl and 4-methyl substituted lactam derivatives steric interactions seem to have a role in forcing the conrotatory process to take place in one sense only: allowing the synthesis of diastereomerically pure compounds to be realized. Because different patterns of substitution on the heterocycle are compatible with the reaction conditions, the methodology developed could be very useful for the synthesis of natural products and biologically active compounds containing cyclopenta-fused O- and N-heterocycle moieties.

Introduction

The Nazarov reaction is the acid-catalyzed cyclization of divinyl ketones **1** to 2-cyclopentenones **2** (Scheme 1) which proceeds, according to stereochemical and spectroscopic studies, through a 4π electrocyclic, conrotatory process (under thermal conditions) involving a pentadienylic intermediate cation.[1,2] Besides dienones of type **1**, a variety of species have been used as precursors for the generation of pentadienyl cations suitable to undergo the electrocyclization, which include α-alkoxy enones, β'-substituted enones, α-vinylcyclobutanones, *gem*-dichlorohomoallyl alcohols, *gem*-dichlorocyclopropylmethanols,

SCHEME 1



vinyl allenes, dienynes, enynol derivatives, and ynediols.[2a,c] Several factors, including the drastic reaction conditions (usually strong acids and high temperature), the poor regioisomeric control, and last but not least, the loss of a

† Dedicated to Prof. Francesco De Sarlo on the occasion of his 65th birthday.

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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.

(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, U.K., 1991; Vol. 5, pp 751−784. (c) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509−8514 and references therein.

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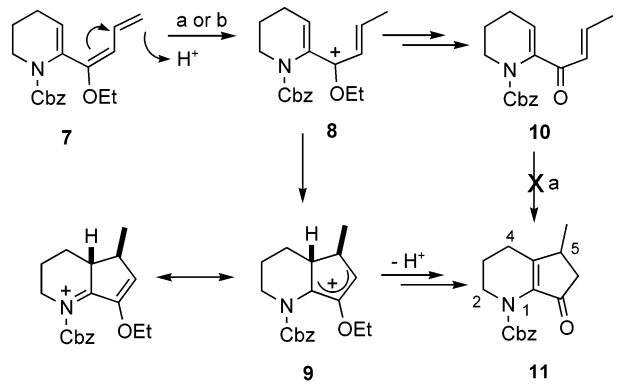
stereocenter in the final step forming **2**, have limited the synthetic applications of this cyclopentannulation process. However, recent improvements such as the use of Lewis acids as cyclization initiators,[3] and procedures called "directed Nazarov cyclization"[4] and "interrupted Nazarov reaction",[5] have expanded the synthetic scopes of the process. The latter methodology, in particular, proved especially useful for the stereoselective construction of polycyclic skeletons by a cascade polycyclization process initiated by a 4π electrocyclic ring closure.[6]

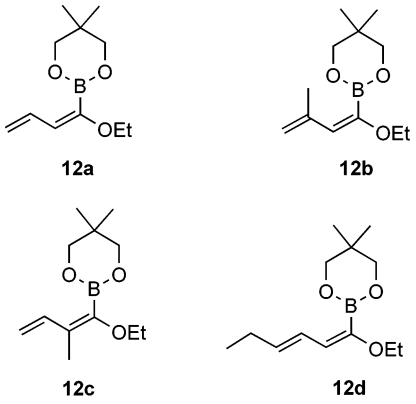
To our knowledge, there are only a few examples of Nazarov reactions carried out with dienones or other precursors of pentadienyl cations in which one of the double bonds is embedded in a nonaromatic heterocyclic structure.[7] A process which involves species such as **3** and **4** (Scheme 1) would certainly be useful for the construction of more complex cyclopenta-fused aza- and oxacycles **5** and **6**, whose structural motif recurs in several natural and biologically active compounds and in intermediates in natural product synthesis.[8] To this end, we have recently shown that conjugated triene **7** (Scheme 2), obtained by Pd-catalyzed cross-coupling reaction of the corresponding lactam-derived vinyl triflate[9a] with α-ethoxydienylboronate **12a**[10] (Chart 1), undergoes

SCHEME 2[a]



[a] Reagents and conditions: (a) Amberlyst 15, $CHCl_3$, 25 °C; (b) 0.02 M HCl, MeOH, 25 °C.

CHART 1



cyclization when treated with the acidic Amberlyst 15 resin in $CHCl_3$ to give the hexahydro[1]pyrindin-7-one derivative **11** in 73% yield after 2 h at room temperature.[9b] For this process we propose a Nazarov-type mechanism which includes protonation of the distal double bond and generation of the 3-alkoxypentadienylic cation **8**, then electrocyclization to form the oxyallyl intermediate **9**, and eventually, loss of a proton to give **11**. A minor product which is formed in this process (less than 5%) is divinyl ketone **10**. The relative amount of **10** increases (up to 35%) if the reaction is carried out with diluted HCl (aq) in methanol, due to a possible trapping of cation **8** by methanol that disrupts the electronic arrangement necessary for the cyclization.

Having already demonstrated that divinyl ketone **10** is not an intermediate in the cyclization process under mild acidic conditions,[9b] a series of questions remained unanswered yet: (a) Is the presence of the N atom (or other heteroatoms) in the cyclic moiety of **7** necessary to attain electrocyclization under the above conditions? (b) Is the reaction outcome dependent on the ring size of the heterocyclic moiety? (c) Is a substituent on the heterocyclic moiety able to affect the torquoselectivity of the process so that only one (or an excess) of the two possible diastereomers is formed? In this paper we try to answer these questions, demonstrating at the same time the synthetic usefulness of the methodology for the diasteroselective synthesis of cyclopenta-fused heterocyclic compounds.

(3) (a) Cooke, F.; Moerck, R.; Schwindeman, J.; Magnus, P. *J. Org. Chem*. **1980**, *45*, 1046−1053. (b) Paquette, L. A.; Dime, D. W.; Fristad, W. E.; Bailey, T. R. *J. Org. Chem*. **1980**, *45*, 3017−3028. (c) Schostarez, H.; Paquette, L. A. *Tetrahedron* **1981**, *37*, 4431−4435.

(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.; Miyiazaki, 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*. **1988**, *63*, 2430−2431.

(6) Bender, J. A.; Arif, A. M.; Giese, S.; West, F. G. *J. Am. Chem. Soc*. **1999**, *121*, 7443−7444.

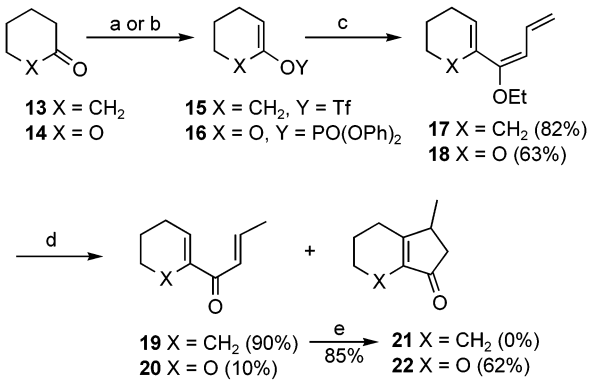
(7) (a) Nazarov, I. N.; Torgov, I. B. *Zh. Obshch. Khim*. **1948**, *18*, 1336. (b) Denmark, S. E.; Habermas, K. L.; Hite, G. A. *Helv. Chim. Acta* **1988**, *71*, 168−194. Examples in which one of the two double bonds is embedded in an aromatic (indole) moiety are known, but it is not clear whether the reaction effectively occurs through a conrotatory 4π electrocyclic process: (c) Ishikura, M.; Imaizumi, K.; Katagiri, N. *Heterocycles* **2000**, *53*, 2201−2220. (d) Miki, Y.; Hachiken, H.; Sugimoto, Y.; Yanase, N. *Heterocycles* **1997**, *45*, 1759−1766. (e) Bergman, J.; Venemalm, L. *Tetrahedron* **1992**, *48*, 759−768. (f) Bergman, J.; Venemalm, L.; Gogoll, A. *Tetrahedron* **1990**, *46*, 6067−6084.

(8) See for example: (a) Kende, A. S.; Hernando, J. I. M.; Milbank, J. B. J. *Org. Lett*. **2001**, *3*, 2505−2508. (b) Harrowven, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron* **2001**, *57*, 791−804. (c) Bramford, S. J.; Luker, T.; Speckamp, W. N.; Hiemstra, H. *Org. Lett*. **2000**, *2*, 1157−1160. (d) Kozikowski, A. P.; Park, P. *J. Org. Chem*. **1990**, *55*, 4668−4682. (e) Gurevich, A. I.; Kolosov, M. N.; Korobto, V. G.; Onoprienko, V. Y. *Tetrahedron Lett*. **1968**, 2209−2212. (f) Gilbert, B.; Duarte, A. P.; Nakagawa, Y.; Joule, J. A.; Flores, S. E.; Brissolese, J. A.; Campello, J.; Carrazzoni, E. P.; Owellen, R. J.; Blossey, E. C.; Brown, K. S., Jr.; Djerassi, C. *Tetrahedron* **1965**, *21*, 1141−1161. Moreover, compounds such as **5** are closely related to or are proline-specific Maillard compounds: (g) Chen, C.-W.; Lu, G.; Ho, C.-T. *J. Agric. Food Chem*. **1997**, *45*, 2996−2999. Examples of compounds having a structure closely related to **5** and **6** that have been used as intermediates in natural product synthesis: (h) Heathcock, C. H.; Norman, M. H.; Dickman, D. A. *J. Org. Chem*. **1990**, *55*, 798−811. (i) Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc*. **1991**, *113*, 2598−2610. (j) Overman, L. E.; Sworin, M.; Bass, L.; Clardy, J. *Tetrahedron* **1981**, *37*, 4041−4045.

(9) (a) Occhiato, E. G.; Trabocchi, A.; Guarna, A. *J. Org. Chem*. **2001**, *66*, 2459−2465. (b) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Deagostino, A.; Venturello, P. *J. Org. Chem*. **2002**, *67*, 7144−7146.

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

SCHEME 3[a]



[a] Reagents and conditions: (a) LHMDS (1 M in THF), HMPA, $PhNTf_2$, THF, −78 °C, 2 h; (b) LHMDS (1 M in THF), HMPA, $(PhO)_2POCl$, THF, −78 °C, 10 min; (c) **12a**, $(Ph_3P)_2PdCl_2$ (5%), THF, 2 M K_2CO_3, 25 °C; (d) Amberlyst 15, $CHCl_3$, 25 °C; (e) neat TFA, 0 °C to room temperature.

Results and Discussion

In the rate-limiting step of the Nazarov reaction depicted in Scheme 1, the change of distribution of the positive charge from the pentadienyl to the 2-hydroxyallyl cation allows one to predict that a suitably positioned substituent on the latter, able to stabilize a positive charge, should accelerate the process.[2a] This could be the case of the electrocyclization of **7** (Scheme 2) in which the charge delocalization on the N atom reasonably lowers the energy of the transition state, thus allowing the process to occur under very mild conditions. To further support this explanation, we synthesized the corresponding carbacycle **17** and oxacycle **18** derivatives (Scheme 3) and subjected them to hydrolysis. Compound **17** was obtained in 82% yield by converting cyclohexanone into the corresponding vinyl triflate **15** and then coupling this with α-ethoxydienylboronate **12a** under $(Ph_3P)_2PdCl_2$ (5%) catalysis in THF at room temperature and in the presence of K_2CO_3 as a base. As for the preparation of compounds such as **18**, functionalization of lactones to afford substituted cyclic vinyl ethers has only recently been investigated.[11] A current methodology involves cyclic ketene acetal triflates as intermediates which, however, often suffer from instability. Thus, we decided to prepare the corresponding lactone-derived vinyl phosphates. Besides the lower cost of the reagents involved in their preparation, these intermediates seem to enjoy higher stability with respect to the corresponding triflates.[12] Cyclic ketene acetal diphenyl phosphate **16** was thus prepared from δ-valerolactone by treatment of its lithium enolate with $(PhO)_2POCl$, in the presence of HMPA, in THF at −78 °C. Vinyl phosphate **16** could be chromatographed and immediately used in the coupling reaction with α-ethoxydienylboronate **12a** under $(Ph_3P)_2PdCl_2$ (5%) catalysis as described above. The reaction was complete in 1 h, affording **18** in 63% yield after chromatography. The hydrolysis of **17** and **18** was performed as usual with Amberlyst 15 in chloroform at room temperature. As a confirmation of the above considerations, treatment of **17** with the acid catalyst gave after 15 h only divinyl ketone **19** (90% yield) and not the corresponding Nazarov product **21**. This was instead obtained in 85% yield by treating **19** with neat TFA at room temperature, that is, under standard electrocyclization conditions for dienones.[13] In contrast, we were pleased to find that hydrolysis of **18** with Amberlyst 15 gave, after 15 h, a separable mixture of Nazarov product **22** (62%) and dienone **20** (10%). As in the case of the aza analogue **7** (see Scheme 2), the presence of the O atom in the cycle seems to accelerate the rate-limiting step (the 4π electrocyclization) of the process by stabilization of the positive charge in the oxyallyl cation intermediate, although the reaction reaches completion in a longer time compared to the hydrolysis of **7**.[9b] A suitably positioned heteroatom in the cycle is therefore mandatory for electrocyclization to occur under mild conditions and at room temperature.

Regarding the second question on the possible effect of the ring size on the reaction outcome, we carried out a series of experiments on five- and seven-membered heterocycles coupled with the α-alkoxy-1,3-dienyl moiety. To this end we prepared *N*-tosyl pyrrolidinone **23** (Scheme 4) in which the presence of the electron-withdrawing N substituent is necessary to ensure stability of the corresponding triflate, as in the case of *N*-Cbz substituted lactam-derived vinyl triflates.

The *N*-tosyl pyrrolidinone **23** was converted into the corresponding triflate **24**[14] through a slight modification of the reported procedure,[15] and this, as a crude material, was directly coupled with α-ethoxydienylboronate **12a** under $(Ph_3P)_2PdCl_2$ (5%) catalysis in THF at 50 °C and in the presence of aqueous 2 M Na_2CO_3 as a base. This sequence afforded **25** in 54% overall yield after chromatography. The hydrolysis of **25** with Amberlyst 15 in $CHCl_3$, however, did not furnish (20 h, rt) the Nazarov product but gave exclusively the corresponding dienone **26** (with the external double bond having *E* stereochemistry) in 84% yield. This result, in strong contrast to that obtained with six-membered heterocycle derivative **7**, could be accounted for by a greater difficulty in the ring closure to give a 5−5 fused system, presumably due to ring strain in the intermediate azabicyclo[3.3.0]octenyl cation.[16] In fact, under classical Nazarov conditions (neat TFA, rt) dienone **26** cyclizes to form the cyclopenta[*b*]-pyrrolone **27** in 64% after 8 h (the yield was 50% when the reaction was carried out with an excess of $MeSO_3H$ in chloroform at room temperature). To demonstrate that

(11) (a) Tsushima, K.; Murai, A. *Chem. Lett.* **1990**, 761−764. (b) Barber, C.; Jarowicki, K.; Kocienski, P. *Synlett* **1991**, 197. (c) Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Tiebes, J.; Sato, M.; Untersteller, E.; Xiao, X.-Y. *J. Am. Chem. Soc.* **1995**, *117*, 1171. (d) Feng, F.; Murai, A.; *Chem. Lett.* **1995**, 23−24. (e) Nicolaou, K. C.; Sato, M.; Miller, N. D.; Gunzner, J. L.; Renaud, J.; Untersteller, E. *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 889.

(12) Nicolaou, K. C.; Shi, G.-Q.; Gunzner, J. L.; Gartner, P.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 5467−5468.

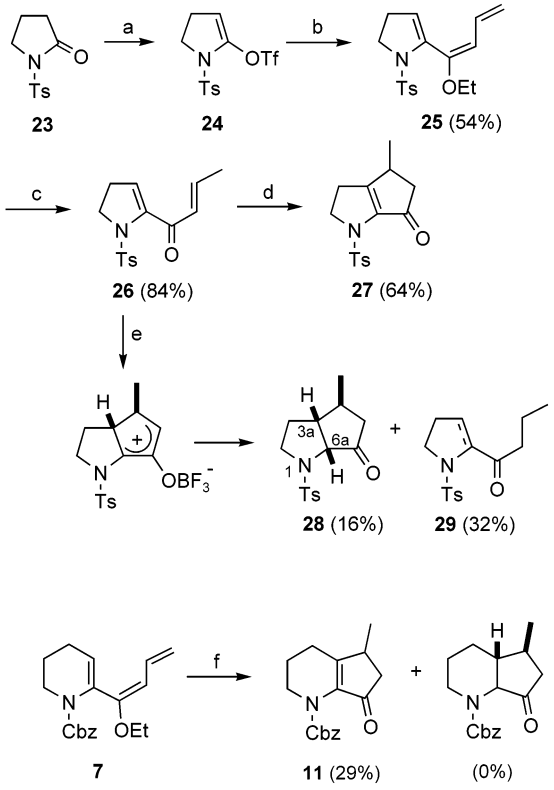
(13) Marino, J. P.; Linderman, R. J. *J. Org. Chem.* **1981**, *46*, 3696−3072.

(14) Compound **24** was stable for at least 24 h in $CDCl_3$ solution.

(15) Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 8131−8140.

(16) This is in accordance with the recent report by West who describes the need for more forcing conditions to effect the tandem Nazarov cyclization [4 + 3]-trapping of a cyclopenta-fused dienone: (a) Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747−2750. Also, the same author has found that solvent trapping of photochemically generated pyran-4-ones does not occur in the case of cyclopenta-fused systems, again because of unacceptable levels of ring strain in the hypothetical oxyallyl zwitterion: (b) Fleming, M.; Fisher, P. V.; Gunawardena, G. U.; Jin, Y.; Zhang, C.; Zhang, W.; Arif, A. M.; West, F. G. *Synthesis* **2001**, 1268−1274.

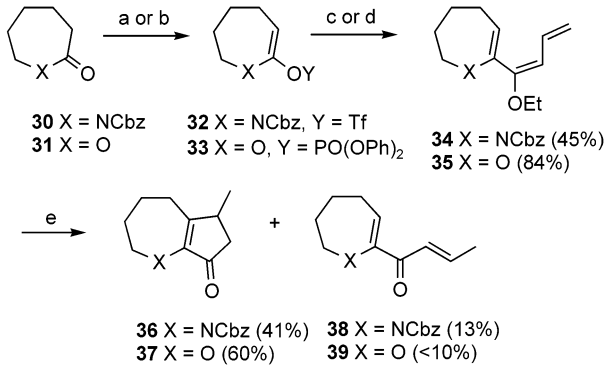
SCHEME 4[a]



[a] Reagents and conditions: (a) KHMDS (0.5 M in toluene), $PhNTf_2$, THF, −78 °C, 1 h; (b) **12a**, $(Ph_3P)_2PdCl_2$ (5%), THF, 2 M Na_2CO_3, 50 °C; (c) Amberlyst 15, $CHCl_3$, 25 °C; (d) neat TFA, 0 °C to room temperature; (e) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, then to 10 °C; (f) Et_3SiH, TFA, CH_2Cl_2, various temperatures.

the latter reaction does actually occur by a 4π electrocyclization, we "interrupted" the process by trapping the intermediate cation under the conditions reported by West (a Lewis acid as a catalyst and Et_3SiH as a hydride donor)[5a] and established the relative stereochemistry of the product. The reaction was carried out by treating a solution of **26** and triethylsilane (2 equiv) in dichloromethane with $BF_3{\cdot}Et_2O$ (1 equiv) at −78 °C, then allowing the mixture to warm to 10 °C. Under these conditions, we were able to isolate by chromatography the product of reduction **28** in 16% yield together with a mixture of open chain products **29** (32%). Low yields were due mainly to decomposition of the starting material, decomposition which was complete when other Lewis acids or TFA were used instead of $BF_3{\cdot}Et_2O$. On the other hand, we managed to assign the cis relative stereochemistry of the methyl group and the bridgehead H3a proton in **28** by a NOE study, which was consistent with the conrotatory pathway of the Nazarov reaction. The cis fusion of **28** was assigned on the basis of the coupling constant between the two bridgehead protons and the NOE cross-peak between H6a and the methyl group. It is interesting to note that by treatment of **26** with BF_3 alone (and other Lewis acids) we were unable to obtain formation of the Nazarov compound **27** but instead observed progressive degradation of the starting material. Therefore, the loss of the proton from the oxyallyl cation intermediate depicted in Scheme 4 (whose formation is demonstrated by the former trapping experiment)

SCHEME 5[a]



[a] Reagents and conditions: (a) LHMDS (1 M in THF), HMPA, $PhNTf_2$, THF, −78 °C; (b) LHMDS (1 M in THF), HMPA, $(PhO)_2POCl$, THF, −78 °C, 10 min; (c) **12a**, $(Ph_3P)_2PdCl_2$ (5%), THF, 2 M Na_2CO_3, 50 °C; (d) **12a**, $(Ph_3P)_2PdCl_2$ (5%), THF, 2 M K_2CO_3, 25 °C; (e) Amberlyst 15, $CHCl_3$, 25 °C.

to give **27** must be a particularly difficult process, although we cannot say whether it limits the reaction rate. The loss of the proton from cationic intermediate **9** (Scheme 2) is instead a fast process, so fast that we were unable to capture this intermediate when we treated **7** (Scheme 4) with an excess of Et_3SiH in TFA. In fact any attempt under a variety of reaction conditions led always to the formation of unsaturated product **11** only (albeit in low yields due to prevailing decomposition of the starting material).

We were interested in verifying if similar difficulties in the Nazarov product formation could be observed with the corresponding oxygenated derivatives, but unfortunately, any effort to synthesize cyclic ketene acetal phosphates from five-membered lactones was unsuccessful, as a consequence of a phosphate−phosphonate rearrangement occurring in the reaction medium even at low temperatures,[17] α-diphenyl phosphonate lactones being the only products recovered.[18] Five-membered lactone-derived vinyl triflates are reported to exhibit labile properties and analogous synthetic problems.[19]

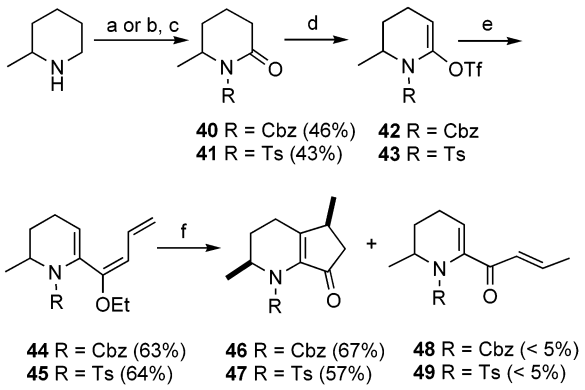
The Nazarov reaction of α-(1-ethoxy-1,3-dienyl) substituted seven-membered heterocycles was carried out with 2,3,4,5-tetrahydro-azepine-1-carboxylic acid benzyl ester and 4,5,6,7-tetrahydro-oxepine derivatives **34** and **35**, respectively (Scheme 5). We have already reported the synthesis and hydrolysis of caprolactam derivative **34**.[9b] In this case the Nazarov cyclization, under Amberlyst 15 catalysis in chloroform, occurred to give **36** in 41% yield. Compared to the hydrolysis of six-membered derivative **7**, the reaction was only slightly slower (4 h) and furnished a higher amount of the α,β-unsaturated ketone **38**. α-Alkoxydienyl derivative **35** was obtained in 84% yield by coupling **12a** with vinyl phosphate **33** (this in turn was prepared as reported above for six-membered derivative **16**) under $(Ph_3P)_2PdCl_2$ (5%) catalysis in THF

(17) We tested γ-butyrolactone, α-angelicalactone, γ-valerolactone, and α-acetil-γ-butyrolactone under different experimental conditions (addition of the base to the lactone or lactone to the base, several molar ratios up to 4 equiv of base, reaction temperatures from −78 °C to room temperature, reaction times from 30 min to 20 h).

(18) Jackson, J. A.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1989**, *54*, 4750−4754.

(19) Tsushima, K.; Araki, K.; Murai, A. *Chem. Lett.* **1989**, 1313−1316.

SCHEME 6[a]

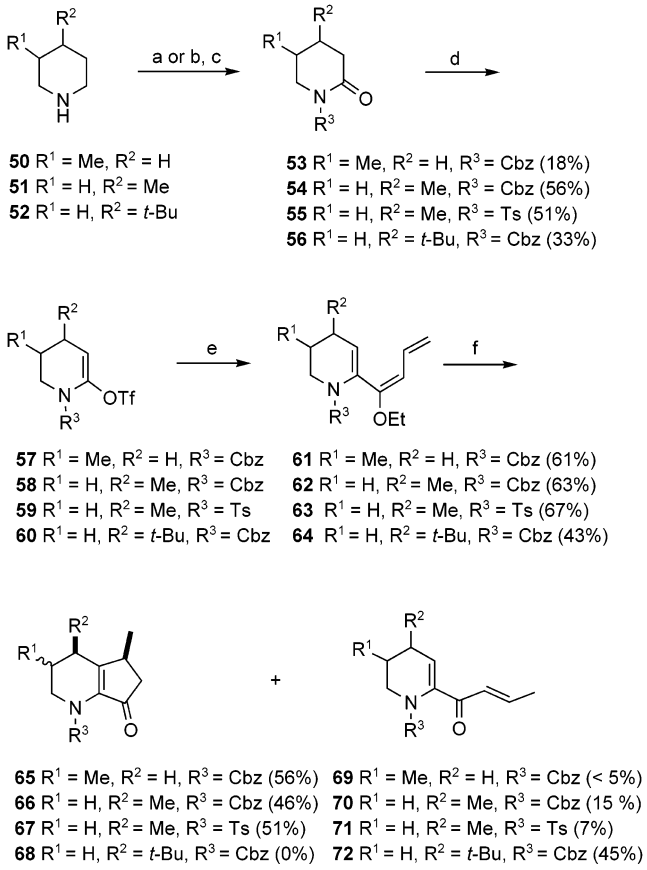


[a] Reagents and conditions: (a) CbzCl, K_2CO_3, THF; (b) TsCl, DMAP, pyridine; (c) $RuO_2{\cdot}xH_2O$, $NaIO_4$, H_2O, ethyl acetate, 25 °C, 2 h; (d) LHMDS (1 M in THF), HMPA, $PhNTf_2$, THF, −70 °C; (e) **12a**, $(Ph_3P)_2PdCl_2$ (5%), THF, 2 M Na_2CO_3, 60 °C; (f) Amberlyst 15, $CHCl_3$, 25 °C.

at room temperature and in the presence of 2 M K_2CO_3 as a base. Hydrolysis of **35** gave, after 17 h, the Nazarov product **37** in 60% yield together with a small amount (less than 10%) of divinyl ketone **39**. On the basis of all of the above experiments, the answer to the second question is, therefore, that the result of the hydrolysis strongly depends on the ring size of the heterocycle bearing the α-alkoxy-1,3-dienyl moiety. Whereas the formation of a fused 5−5 system does not take place unless classical Nazarov conditions are used with a divinyl ketone such as **26**, six- and seven-membered lactam and lactone derivatives easily undergo electrocyclization under milder conditions to give 6−5 and 7−5 fused heterocycles in good yield.[20]

It has been shown that the factors that control the sense of torquoselectivity in the Nazarov reaction are primarily steric in origin,[2a,21] which favor an approach to the less-hindered face of the endocyclic olefin and lead to a prevailing clockwise (*R*) or counterclockwise (*S*) rotation when viewed down the C−O bond. In our case, the problem of the diastereoselection in the ring closure was dealt with by using 2-, 3-, and 4-alkyl substituted lactam derivatives **44**, **45** (Scheme 6), and **61**−**64** (Scheme 7). These compounds were obtained starting from racemic 2-methylpiperidine and piperidines **50**−**52**. These were protected as *N*-Cbz or *N*-Ts derivatives and oxidized to the corresponding lactams **40**, **41** (Scheme 6), and **53**−**56** (Scheme 7) by hydrated RuO_2 in the presence of $NaIO_4$.[22,23] The coupling of the corresponding vinyl triflates with α-alkoxydienylboronate **12a** was carried as usual and afforded trienes **44**, **45** (Scheme 6), and **61**−**64** (Scheme 7) in good yields (61−67% after chromatographic purification). The hydrolysis of **44** was carried

SCHEME 7[a]



[a] Reagents and conditions: (a) CbzCl, K_2CO_3, THF; (b) TsCl, DMAP, pyridine; (c) $RuO_2{\cdot}xH_2O$, $NaIO_4$, H_2O, ethyl acetate, 25 °C, 2 h; (d) LHMDS (1 M in THF), HMPA, $PhNTf_2$, THF, −70 °C; (e) **12a**, $(Ph_3P)_2PdCl_2$ (5%), THF, 2 M Na_2CO_3, 60 °C; (f) Amberlyst 15, $CHCl_3$, 25 °C.

out as usual with Amberlyst 15. It was complete in 18 h (being thus slower than that of unsubstituted triene **7**) and afforded, after chromatography, only a single Nazarov compound (**46**) in 67% yield (together with a small amount of the divinyl ketone **48**) which had the two methyl groups incorporated in a cis relationship. This structural assignment was based on a complete NMR analysis of **46**. In particular, NOESY cross-peaks between the two methyl groups and the same proton on C4 were consistent with the cis relative stereochemistry. This result was confirmed by the hydrolysis of the corresponding triene **45** in which the N atom bears a tosyl group. The hydrolysis of **45** was carried out with Amberlyst 15 in chloroform at room temperature and was complete in 18 h. ^{1}H NMR of the crude reaction mixture revealed the presence of two products, one being the Nazarov compound **47** (isolated in 57% yield after chromatography) and the second α,*β*-unsaturated ketone **49** (less than 5%). A NOE study on **47** suggested again the cis relative stereochemistry of the two methyl groups, because both have a diagnostic cross-peak with the same proton on C4. In this case, the relative stereochemistry was confirmed by X-ray analysis of **47** (see the Supporting Information).

When 4-methyl substituted trienes **62** and **63** (Scheme 7) were treated with Amberlyst 15 in chloroform, the hydrolysis again yielded, after 24 h at 25 °C, single

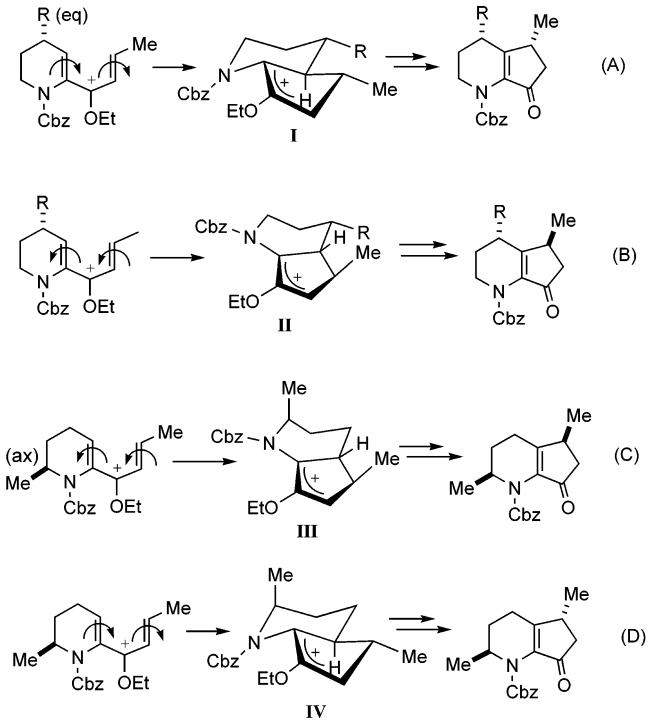
(20) In the case of product **35**, hydrolysis conditions must be carefully controlled in order to avoid the side hydrolysis of the cyclic vinyl ether moiety with subsequent opening of the seven-membered cycle. In this case (7*E*)-7-ethoxy-7,9-decadien-1-ol was recovered.

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

(22) Kozlowski, M. C.; Xu, Z.; Gil Santos, A. *Tetrahedron* **2001**, *57*, 4537−4542.

(23) The oxidation was carried out on the crude mixtures obtained after workup of the N protection reactions. Although the overall yields were not satisfactory, we did not try at this stage to optimize them or evaluate other procedures to obtain these lactams.

SCHEME 8



diasteroisomers (**66** and **67** in 46% and 51% yield, respectively) in which the two methyl groups have a cis relative stereochemistry, together with a higher than usual amount of the corresponding dienones. The structural assignment was possible because of bidimensional NOESY spectra in which a diagnostic cross-peak between the signals attributable to H4 and H5 was found.[24]

The increase in steric bulk of the 4-substituent on the lactam seems to prevent the formation of the Nazarov compound during the hydrolysis: when 4-*tert*-butyl derivative **64** (Scheme 7) was treated with Amberlyst 15 in chloroform at room temperature, the hydrolysis afforded exclusively α,β-unsaturated ketone **72** (45% yield).

We also prepared and hydrolyzed, according to the usual strategy, 3-methyl substituted triene **61**. In this case we observed the formation of an inseparable ~1.2:1 mixture of the two diastereomers (**65**) in 56% yield.

In accordance with Denmark's results about silicon-directed Nazarov cyclizations,[21] our findings suggest that steric interactions play a role in the selection between the two possible conrotatory pathways and lead to the formation of the cis diastereomer for both 2-methyl and 4-methyl substituted derivatives, as depicted in Scheme 8. In the case of C4 substituted trienes, we may assume that the more stable conformer is that in which the R group on C4 is equatorial. A conrotatory clockwise electrocyclization (path A) would involve the upper face (i.e., the less hindered one) of the endocyclic olefin with the formation of transition structure **I** that, after proton loss, gives cis product **66** (similarly for *N*-Ts derivative **67**). This approach could be further favored because it would lead to a chairlike conformation of the six-membered ring in the transition structure **I** as C5 rehybridizes. A similar argument was made with regard to the photo-Nazarov ring contraction of a fused bicyclic 4-pyrone.[16b] In the case of a counterclockwise mode of conrotation (path B), not only does the bond formation involve the more hindered face of the endocyclic double bond but it leads to an unfavorable transition structure **II** in which the six-membered ring is a twist-boat conformation. The selectivity obtained in the cyclization of 4-methyl substituted trienes **62** and **63** is in accordance with that found in the silicon-directed cyclization of carbacyclic dienones in which ratios up to 94:6 were measured in favor of the cis diastereomer.[21] In the hydrolysis of 4-*tert*-butyl substituted derivative **64**, the steric repulsion between the two alkyl groups in transition structure **I** could hamper cyclization.

Concerning the 2-methyl substituted derivatives, it is known that in piperidines which bear a carboalkoxy or a tosyl group on the N atom, 2-alkyl substituents are preferentially pseudoaxially oriented in order to reduce the allylic strain with the N protecting group. Much chemistry has been indeed based on this feature that strongly affects the stereochemical outcome of additions to the enamine double bond.[25] Referring to Scheme 8, a counterclockwise conrotatory cyclization would involve the less hindered face (i.e., that opposite to the axially oriented 2-methyl) and lead to the formation of the cis product (path C). This conrotation, however, imposes a six-membered twist-boat conformation in transition structure **III**, whereas a clockwise conrotation (path D) would lead to a six-membered chair conformation (in **IV**) and then to the trans product. If we assume that the 2-methyl group is axially oriented (this is certain for the final products; see the X-ray crystallographic structure determination of **47**), then the exclusive formation of cis products **46** and **47** suggests that these cyclizations take place under steric control. On the basis of this consideration, the low remote stereocontrol exerted by the 3-methyl group in the hydrolysis of **61** could be due to the equatorial orientation and distance of this methyl group from the reacting C5 center, the two faces of the endocyclic olefin being thus not sterically differentiated and both modes of conrotation possible.

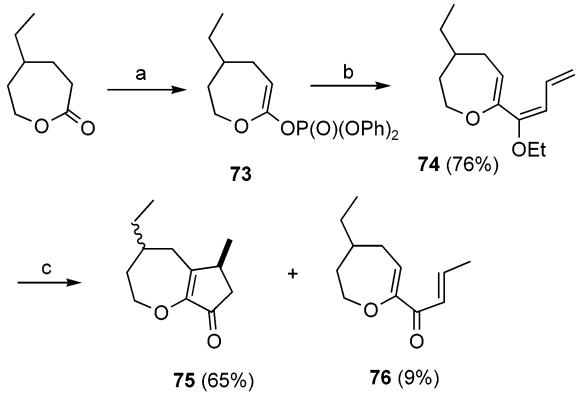
Analogously, lack of a complete diastereoselection was observed in the Nazarov cyclization on triene **74** (Scheme 9). We prepared 3-ethyl-ϵ-caprolactone starting from 4-ethyl-cyclohexanone according to a Baeyer−Villiger procedure.[26] Ketene acetal phosphate **73** was synthesized as usual and chromatographed, proving to be quite stable

(24) The assignment of the cis relative stereochemistry to **66** (and **67**) was complicated by the overlap of some signals in the ^{1}H NMR spectrum. In particular, the two methyl groups resonate very close at 1.14 and 1.11 ppm which hampers the determination of their relative orientation by NOE studies. On the other hand, the signals of H4 (2.61 ppm) and H5 (2.86 ppm) are distinct but that of H4 in part overlaps with the signal (at 2.65 ppm) of a proton on C6. To distinguish between scalar and spatial interactions, a series of NOESY spectra were recorded by progressively changing the mixing time. In this way a NOESY cross-peak between H4 and H5 could be identified. Derome, A. E. *Modern NMR Techniques for Chemistry Reserach*; Pergamon Press: Oxford, U.K., 1987.

(25) (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.

(26) Canan Koch, S. S.; Chamberlin, A. R. *Synth. Commun.* **1989**, *19* (5−6), 829−834.

SCHEME 9[a]



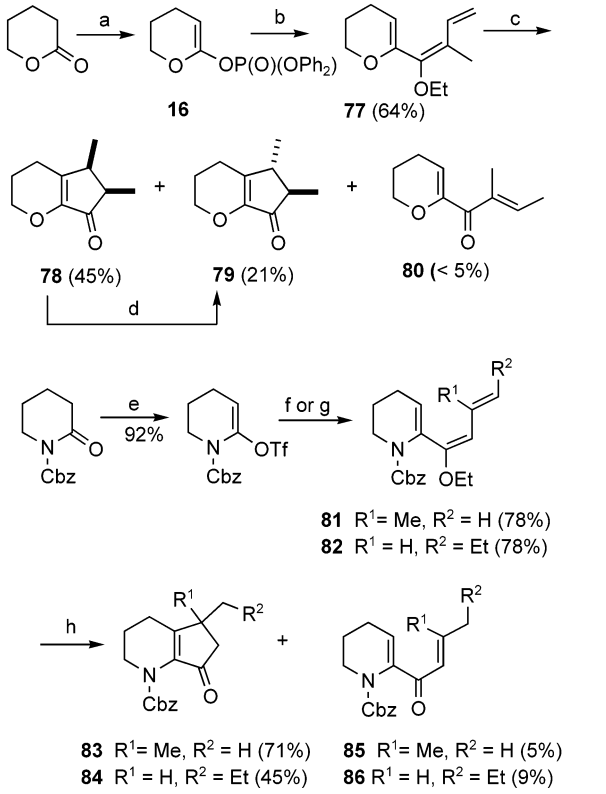
[a] Reagents and conditions: (a) LHMDS (1 M in THF), HMPA, $(PhO)_2POCl$, THF, −78 °C; (b) **12a**, $(Ph_3P)_2PdCl_2$ (5%), THF, 2 M K_2CO_3, 25 °C; (c) Amberlyst 15, $CHCl_3$, 25 °C.

for the successive cross-coupling reaction step. The coupling reaction was carried out at room temperature with $(Ph_3P)_2PdCl_2$ as a catalyst and afforded **74** in 76% yield after chromatography. The hydrolysis of **74** gave a mixture of two diasteromeric Nazarov compounds **75** (65% yield) in a 3:1 ratio (GC) and a smaller amount (less than 10%) of open chain compound **76**. Again, as in the case of **61** (Scheme 7), the substituent on the heterocycle does not sufficiently differentiate the two faces of the endocyclic double bond to induce a unique mode of conrotation in the cyclization process.

With the last series of experiments, we were able to answer to the third question initially raised regarding the torquoselectivity of the 4π electrocyclization of our trienes. A related question concerns the relative stereochemistry of two groups on the newly created cyclopentenone ring when suitably substituted α-alkoxydienylboronates are used as coupling partners.

For this issue we used δ-valerolactone as the starting material to prepare triene **77** (64% yield, Scheme 10) by coupling the corresponding vinyl phosphate **16** with 2-methyl substituted α-ethoxydienylboronate **12c** (Chart 1) according to the usual methodology. The hydrolysis of **77** furnished, after 18 h at room temperature, two diastereomeric Nazarov products **78** (45%) and **79** (21%), together with α,β-unsaturated ketone **80** (less than 5% yield). The two diastereomers were separated by flash chromatography and fully characterized. ^{1}H NMR analysis of the two heterobicycles allowed us to establish that the major compound has a cis relative stereochemistry. The ^{1}H NMR of **78** shows a pentuplet (J = 6.2 Hz) at 2.82 ppm attributable to H6. The coupling constant value between H6 and H5 (6.2 Hz) suggests a relative cis stereochemistry. In **79**, H6 appears as a quartet of doublets at 2.26 ppm (with J = 7.0, 1.8 Hz). The small value of $J_{H5/H6}$ (1.8 Hz) is characteristic of a trans stereochemistry in these fused five-membered cycles. Whereas a 30 min treatment of cis product **78** with KOH in methanol led to the formation of a 3:2 mixture of the two epimers **78** and **79**, a similar treatment of trans product **79** left the compound unaltered. This experiment suggests that the final hydrolytic step of the process does not afford a thermodynamic mixture.

SCHEME 10[a]



[a] Reagents and conditions: (a) LHMDS (1 M in THF), HMPA, $(PhO)_2POCl$, THF, −78 °C, 10 min; (b) **12c**, $(Ph_3P)_2PdCl_2$ (5%), THF, 2 M K_2CO_3, 25 °C; (c) Amberlyst 15, $CHCl_3$, 25 °C; (d) KOH, MeOH, 25 °C 30 min; (e) LHMDS (1 M in THF), HMPA, $PhNTf_2$, THF, −78 °C; (f) **12b**, $(Ph_3P)_2PdCl_2$ (5%), THF, 2 M Na_2CO_3, 50 °C; (g) **12d**, $(Ph_3P)_2PdCl_2$ (5%), THF, 2 M K_2CO_3, 25 °C; (h) Amberlyst 15, $CHCl_3$, 25 °C.

Finally, α-alkoxydienylboronates **12b** and **12d** (Chart 1) were used to obtain pyrindinones bearing different substituents on the cyclopentenone moiety. The synthesis of compound **83** (Scheme 10) has been already described by us.[9b] Compound **82** was prepared according to the usual methodology and gave, after hydrolysis, the Nazarov product **84** in 45% yield after chromatography.

Conclusion

In conclusion we have developed a new synthetic route to cyclopenta-fused N- and O-containing heterocycles which is based on the initial Pd-catalyzed coupling reaction between lactam or lactone-derived vinyl triflates and phosphates and α-alkoxydienylboronates, followed by the Nazarov reaction of the coupling products under mild acidic conditions. Besides finding the conditions for the functionalization of lactams and lactones by Pd-catalyzed reactions, the major effort has been that of gaining a deeper insight into the electrocyclization process. With this purpose we focused on the close examination of the role and effect of the heteroatom and heterocycle ring size on the reaction outcome and the effect of the substituents on the torquoselectivity during the ring closure step. As regards the first question, we demonstrated that the presence of a heteroatom such as N or O is essential in stabilizing the incipient oxyallyl cation in the transition state of the process. In fact,

analogue carbacycle trienes, under the mild hydrolysis conditions used, did not afford the Nazarov cyclization product but only the open chain ketone. The ring size is a basic parameter in the cyclization step as well: five-membered azacycles require more drastic conditions to give 5−5 fused systems and do so only after initial hydrolysis to obtain the corresponding divinyl ketone; otherwise, six- and seven-membered heterocycles undergo electrocyclization under very mild conditions. Concerning the torquoselectivity, with 2-methyl and 4-methyl substituted lactam derivatives steric interactions seem to have a role in forcing the conrotatory process to take place in one sense only: allowing the synthesis of diastereomerically pure compounds to be realized. A lower stereocontrol was instead exerted by differently positioned substituents. Because different patterns of substitution on the heterocycle are compatible with the reaction conditions, the methodology proposed could be very useful for the synthesis of target natural products and biologically active compounds containing cyclopenta-fused O- and N-heterocycle moieties. Ongoing studies are aimed at establishing the torquoselectivity of the process with six-membered lactone derivatives.

Experimental Section

All solvents were degassed before use in cross-coupling processes. Chromatographic separations were carried out under pressure on silica gel using flash-column techniques; R_f values refer to TLC carried out on 0.25 mm silica gel plates, with the same eluant as that indicated for the column chromatography. ^{1}H NMR spectra were recorded at 400 and 200 MHz, NOESY and NOE experiments at 400 MHz, and ^{13}C NMR spectra at 100.4 and 50.33 MHz. MS spectra were recorded at an ionizing voltage of 70 eV. Boronates **12a**−**d** were prepared as reported.[10] Compounds **11**, **36**, and **83** are known.[9b] *N*-Tosylpyrrolidinone **23** was prepared according to a reported procedure.[15] 5-Ethyl oxepan-2-one was synthesized according to the literature.[26] The syntheses of compounds **15**,[27] **19**,[2a,28] and **21**[2a,3b] have already been reported. The synthesis of 4-methyl-tetrahydropyran-2-one has been realized as reported.[29] Chloroform used for the hydrolysis with Amberlyst 15 was dried over anhydrous sodium sulfate. THF was distilled from Na/benzophenone, and CH_2Cl_2 was distilled from CaH_2 prior reaction.

Trifluoromethanesulfonic Acid Cyclohex-1-enyl Ester (15). To a cold solution (−78 °C) of cyclohexanone (0.49 g, 5 mmol) and HMPA (1.31 mL, 7.5 mmol) in THF (10 mL), lithium bis(trimethylsilyl)amide (LHMDS, 1 M solution in THF, 6 mL, 6 mmol) was added over a period of 10 min. Afterward, a solution of $PhNTf_2$ (1.9 g, 5 mmol) in 4 mL of THF was added, the reaction mixture was stirred for an additional 2 h, and then the reaction was quenched with a 10% solution of NaOH. The mixture was extracted with Et_2O (3 × 20 mL), washed with water (3 × 20 mL), and dried over anhydrous K_2CO_3. After filtration and evaporation of the solvent, crude vinyl triflate **15** was obtained and, in part, directly used for next coupling reaction. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 5.65 (br s, 1 H), 2.40−2.20 (m, 4 H), 1.95−1.85 (m, 2 H), 1.75−1.65 (m, 2 H).

Phosphoric Acid 5,6-Dihydro-4*H*-pyran-2-yl Ester Diphenyl Ester (16). To a cold solution (−78 °C) of diphenylphosphoryl chloride (1.55 mL, 7.5 mmol), δ-valerolactone (500 mg, 5 mmol), and HMPA (1.31 mL, 7.5 mmol) in THF (10 mL), was added lithium bis(trimethylsilyl)amide (LHMDS, 6 mL of a 1 M solution in THF, 6 mL) over a period of 10 min. The reaction mixture was stirred at −78 °C for an additional 10 min before it was diluted with diethyl ether (20 mL). The organic solution was then stirred with 5% aqueous ammonia solution (30 mL) for 15 min. The organic phase was separated, and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined ethereal extracts were dried and concentrated and the residue chromatographed (Et_2O−petroleum ether 1:1, 0.5% Et_3N, R_f = 0.62) to give 1.36 g of **16** (82% yield) as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.15−6.85 (m, 10 H), 4.20 (m, 1 H), 3.82 (t, J = 6.5 Hz, 2 H), 1.90−1.74 (m, 2 H), 1.60−1.40 (m, 2 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 173.9 (s), 152.3 (s, 2 C), 130.9 (d, 4 C), 125.9 (d, 2 C), 120.7 (d, 4 C), 82.2 (d), 64.5 (t), 34.3 (t), 22.9 (t). MS *m*/*z*: 332 (M^+, 97), 249 (33), 170 (24), 117 (34), 77 (44), 55 (100).

(*E*)-1-(1-Ethoxybuta-1,3-dienyl)-cyclohexene (17). To a solution of α-ethoxydienylboronate **12a** (105 mg, 0.5 mmol) in THF (10 mL) were added, under argon atmosphere, $(Ph_3P)_2PdCl_2$ (17 mg, 0.024 mmol), triflate **15** (115 mg, 0.5 mmol), and aqueous 2 M K_2CO_3 (0.5 mL). The mixture was stirred at room temperature for 30 min until the reagents had dissappeared as determined by TLC monitoring. The mixture was then extracted with Et_2O (20 mL), washed with water, and dried over anhydrous potassium carbonate. After evaporation of the solvent, crude products were purified by flash chromatography (Et_2O−petroleum ether 1:9, 0.5% Et_3N, R_f = 0.85) to give pure **17** as a pale yellow oil (73 mg, 82%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 6.50 (dt, J = 16.0, 10.0 Hz, 1 H), 5.81 (br s, 1 H), 5.35 (d, J = 10.0 Hz, 1 H), 5.00 (dd, J = 16.0, 1.0 Hz, 1 H), 4.76 (dd, J = 10.0, 1.0 Hz, 1 H), 3.75 (q, J = 7.3 Hz, 2 H), 2.10−2.21 (br s, 4 H), 1.60−1.75 (m, 4 H), 1.13 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 161.9 (s), 133.8 (s), 131.0 (d), 115.5 (d), 111.0 (t), 102.7 (d), 63.6 (t), 27.3 (t), 25.9 (t), 23.2 (t), 22.7 (t), 15.9 (q). MS *m*/*z*: 178 (M^+, 62), 136 (94), 107 (100). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.61; H, 10.36.

(*E*)-6-(1-Ethoxybuta-1,3-dienyl)-3,4-dihydro-2*H*-pyran (18). The above-reported procedure for **17** was used to prepare **18** starting from phosphate **16** (166 mg, 0.5 mmol). The reaction was complete in 1 h. After purification by flash chromatography (Et_2O−petroleum ether 1:9, 0.5% Et_3N, R_f = 0.74), pure **18** was obtained as a pale oil (57 mg, 63%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 6.83 (dt, J = 16.0, 10.0 Hz, 1 H), 5.50 (d, J = 10.0 Hz, 1 H), 5.13 (t, J = 6.5 Hz, 1 H), 5.00 (dd, J = 16.0, 1.0 Hz, 1 H), 4.80 (dd, J = 10.0, 1.0 Hz, 1 H), 4.18 (t, J = 6.5 Hz, 2 H), 3.83 (q, J = 7.3 Hz, 2 H), 2.12−2.25 (m, 2 H), 1.79−1.92 (m, 2 H), 1.34 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 152.9 (s), 149.2 (s), 134.1 (d), 113.4 (t), 106.4 (d), 103.8 (d), 66.8 (t), 64.2 (t), 22.7 (t), 21.2 (t), 15.3 (q). MS *m*/*z*: 180 (M^+, 100), 151(53), 123 (68), 95 (68). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.44; H, 8.68.

1-Cyclohex-1-enyl-but-2-en-1-one (19). To a solution of **17** (89 mg, 0.5 mmol) in anhydrous $CHCl_3$ (7 mL) under argon atmosphere, Amberlyst 15 (2.3 mequiv/g, 18 mg) was added, and the resulting mixture was stirred at room temperature. The reaction was monitored by TLC. After 15 h the resin was filtered off through a short pad of $NaHCO_3$ and the solution was concentrated under vacuum. Crude products were purified by flash chromatography (Et_2O−petroleum ether 1:1, 0.5% Et_3N, R_f = 0.7) to give pure **19** (67 mg, 90%). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 6.95−6.80 (m, 2 H), 6.55 (d, J = 16.2 Hz, 1 H), 2.35−2.16 (m, 4 H), 1.85 (dd, J = 7.5, 1.5 Hz, 3 H), 1.53−1.50 (m, 4 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 192.0 (s), 142.6 (d), 141.3 (s), 140.5 (d), 127.2 (d), 26.8 (t), 23.8 (t), 22.7 (t), 22.2 (t), 19.0 (q). MS *m*/*z*: 150 (M^+, 47), 135 (97), 41 (100).

3-Methyl-2,3,4,5,6,7-hexahydro-inden-1-one (21). Pure **19** (67 mg, 0.44 mmol) was dissolved in neat TFA (2.5 mL) at 0 °C and stirred at room temperature. After 6 h the reaction was complete (by TLC), and the mixture was diluted with Et_2O (20 mL) and washed with a 5% aqueous solution of $NaHCO_3$, and the organic layer was dried over K_2CO_3. After evaporation

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of the solvent, crude product was chromatographed (Et_2O−petroleum ether, 1:1, 0.5% Et_3N, $R_f = 0.7$) to give pure **21** (56 mg, 85%) as a white oil. ^1H NMR (200 MHz, $CDCl_3$, δ): 2.72 (pent, $J = 6.5$ Hz, 1 H), 2.62 (dd, $J = 18.3$, 6.5 Hz, 1 H), 2.30−2.10 (m, 3 H), 1.95 (d, $J = 18.3$ Hz, 1 H), 1.75−1.62 (m, 5 H), 1.15 (d, $J = 6.5$ Hz, 3 H). MS *m*/*z*: 150 (M^+, 26), 69 (100).

5-Methyl-3,4,5,6-tetrahydro-2*H*-cyclopenta[*b*]pyran-7-one (22). This compound was obtained as described for **19** starting from **18** (57 mg, 0.31 mmol). Flash chromatography (Et_2O−petroleum ether 1:1, 0.5% Et_3N) gave pure **22** (29 mg, 62%, $R_f = 0.33$) and **20** (8 mg, 10%, $R_f = 0.53$), both as oils.

22. ^1H NMR (400 MHz, $CDCl_3$, δ): 4.05 (m, 1 H), 3.98 (m, 1 H), 2.64 (m, 1 H), 2.56 (dd, $J = 18.3$, 6.2 Hz, 1 H), 2.34 (dt, $J = 18.3$, 6.5 Hz, 1 H), 2.14 (dt, $J = 18.3$, 6.5 Hz, 1 H), 1.92−1.87 (m, 3 H), 1.11 (d, $J = 7.0$ Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 200.2 (s), 159.4 (s), 150.1 (s), 66.8 (t), 41.7 (t), 32.1 (d), 21.9 (t), 21.6 (t), 19.3 (q). MS *m*/*z*: 152 (M^+, 91), 137 (100). Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.26; H 7.97.

20. ^1H NMR (200 MHz, $CDCl_3$, δ): 6.94 (dq, $J = 16.1$, 7.5 Hz, 1 H), 6.65 (d, $J = 16.1$ Hz, 1 H), 6.15 (m, 1 H), 4.15−4.10 (m, 2 H), 2.30−2.15 (m, 2 H), 1.91 (dd, $J = 7.5$, 1.5 Hz, 3 H), 1.95−1.75 (m, 2 H). ^{13}C NMR ($CDCl_3$, δ): 195.2 (s), 165.1 (s), 148.3 (d), 134.1 (d), 112.3 (d), 71.2 (t), 34.2 (t), 26.8 (t), 16.0 (q). MS *m*/*z*: 152 (M^+, 26), 69 (100).

Trifluoromethanesulfonic Acid 1-(Toluene-4-sulfonyl)-4,5-dihydro-1*H*-pyrrol-2-yl Ester (24). To a solution of KHMDS (5.2 mL of a 0.5 M solution in toluene, 2.6 mmol) in THF (12 mL), cooled to −78 °C and maintained under nitrogen atmosphere, was added a solution of *N*-tosylpyrrolidinone **23** (500 mg, 2.08 mmol) in THF (4 mL), and the resulting mixture was stirred for 1.5 h. Afterward, a solution of $PhNTf_2$ (928 mg, 2.6 mmol) in THF (2 mL) was quickly added, and the reaction mixture was stirred for 1 h at −78 °C before the temperature was allowed to rise to 0 °C. Then, a 10% NaOH solution (20 mL) was added, and the mixture was extracted with Et_2O (3 × 20 mL), washed with water (2 × 10 mL), and dried over anhydrous K_2CO_3. After filtration and evaporation of the solvent, crude vinyl triflate **24** was obtained as a yellowish oil and directly used for the next coupling reaction. ^1H NMR (200 MHz, $CDCl_3$, δ): 7.75 (d, $J = 8.4$ Hz, 2 H), 7.34 (d, $J = 8.4$ Hz, 2 H), 5.10 (t, $J = 2.9$ Hz, 1 H), 3.87 (t, $J = 8.1$ Hz, 2 H), 2.44 (s, 3 H), 2.23 (td, $J = 8.1$, 2.9 Hz, 2 H).

5-(1-Ethoxybuta-1,3-dienyl)-1-(toluene-4-sulfonyl)-2,3-dihydro-1*H*-pyrrole (25). To a solution of crude **24** (2.08 mmol) in THF (24 mL) were added, under a nitrogen atmosphere, $(Ph_3P)_2PdCl_2$ (66 mg, 0.09 mmol), boronate **12a** (466 mg, 2.22 mmol), and a 2 M aqueous Na_2CO_3 solution (14 mL). The mixture was stirred for 2.5 h at 50 °C. Water (50 mL) was then added, and the mixture was extracted with diethyl ether (3 × 40 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded a yellow oil which was purified by chromatography (EtOAc−petroleum ether 1:4, 0.5% Et_3N, $R_f = 0.44$) to give **25** (361 mg, 54%) as a colorless oil. ^1H NMR (200 MHz, $CDCl_3$, δ): 7.67 (d, $J = 8.1$ Hz, 2 H), 7.23 (d, $J = 8.1$ Hz, 2 H), 6.38 (ddd, $J = 15.0$, 11.0, 10.2 Hz, 1 H), 5.59 (d, $J = 11.0$ Hz, 1 H), 5.34 (t, $J = 2.9$ Hz, 1 H), 5.06 (dd, $J = 15.0$, 1.8 Hz, 1 H), 4.81 (dd, $J = 10.2$, 1.8 Hz, 1 H), 3.95−3.78 (m, 2 H + 2 H), 2.38 (s, 3 H), 2.20 (td, $J = 8.8$, 2.9 Hz, 2 H), 1.32 (t, $J = 6.9$ Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 150.1 (s), 143.6 (s), 137.5 (s), 134.0 (s), 133.1 (d), 129.4 (d, 2 C), 128.0 (d, 2 C), 120.4 (d), 112.8 (t), 107.2 (d), 63.9 (t), 49.8 (t), 28.1 (t), 21.4 (q), 14.5 (q). MS *m*/*z*: 319 (M^+, 9), 164 (55), 90 (100). Anal. Calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39. Found: C, 64.19; H, 6.44; N, 4.01.

1-[1-(Toluene-4-sulfonyl)-4,5-dihydro-1*H*-pyrrol-2-yl]-but-2-en-1-one (26). To a solution of **25** (361 mg, 1.13 mmol) in $CHCl_3$ (8 mL) was added Amberlyst 15 (103 mg), and the resulting mixture was stirred at room temperature and monitored by TLC. After 6 h another 47 mg of Amberlyst 15 was added and the mixture was stirred for a further 14 h. The mixture was then filtered through a short pad of $NaHCO_3$ and concentrated. The residue was chromatographed (EtOAc−petroleum ether 1:4, $R_f = 0.18$) to give pure **26** (276 mg, 84%) as a colorless oil. ^1H NMR (200 MHz, $CDCl_3$, δ): 7.62 (d, $J = 8.4$ Hz, 2 H), 7.24 (d, $J = 8.4$ Hz, 2 H), 7.00 (dq, $J = 17.2$, 6.9 Hz, 1 H), 6.56 (d, $J = 17.2$ Hz, 1 H), 6.01 (t, $J = 2.9$ Hz, 1 H), 3.81 (t, $J = 8.4$ Hz, 2 H), 2.36 (s, 3 H), 1.99 (td, $J = 8.4$, 2.9 Hz, 2 H), 1.89 (d, $J = 6.9$ Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 185.5 (s), 144.8 (s), 144.2 (s), 143.9 (d), 129.5 (d, 2 C), 129.2 (d), 128.0 (d, 2 C), 127.2 (d), 126.9 (s), 50.7 (t), 28.5 (t), 21.5 (q), 18.3 (q). MS *m*/*z*: 291 (M^+, 2), 136 (72), 91 (100). Anal. Calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81. Found: C, 61.79; H, 5.72; N, 4.63.

4-Methyl-1-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-1*H*-cyclopenta[*b*]pyrrol-6-one (27). A solution prepared by dissolving **26** (62 mg) in neat TFA (2 mL) at 0 °C was allowed to warm to room temperature while being stirred. The initially colorless solution turned yellow and then progressively deepened toward dark-red. After 8 h the reaction was complete (by TLC) and the mixture was diluted with Et_2O (20 mL). Then it was washed with a saturated aqueous $NaHCO_3$ solution until gas evolution ceased, and the organic layer was dried over sodium sulfate. After evaporation of the solvent, the crude oil was chromatographed (EtOAc−petroleum ether 1:1, 0.5% Et_3N, $R_f = 0.37$) to give **27** (40 mg, 64%) as a yellowish oil. ^1H NMR (200 MHz, $CDCl_3$, δ): 7.78 (d, $J = 8.1$ Hz, 2 H), 7.27 (d, $J = 8.1$ Hz, 2 H), 4.19 (t, $J = 9.2$ Hz, 2 H), 2.95 (dd, $J = 18.3$, 5.9 Hz, 1 H), 2.74 (m, 1 H), 2.70−2.40 (m, 2 H), 2.39 (s, 3 H), 2.30 (d, $J = 18.3$ Hz, 1 H), 1.06 (d, $J = 7.0$ Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 191.6 (s), 145.1 (s), 143.8 (s), 134.7 (s), 129.5 (d, 2 C), 127.9 (d, 2 C), 126.9 (s), 56.0 (t), 49.4 (t), 29.7 (d), 27.0 (t), 21.6 (q), 18.8 (q). MS *m*/*z*: 291 (M^+, 43), 90 (100). Anal. Calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81. Found: C, 61.92; H, 5.56; N, 4.69.

4-Methyl-1-(toluene-4-sulfonyl)-hexahydrocyclopenta-[*b*]pyrrol-6-one (28). To a stirred solution of **26** (114 mg, 0.39 mmol) in CH_2Cl_2 (20 mL), cooled to −78 °C and maintained under nitrogen atmosphere, were added Et_3SiH (125 μL, 0.78 mmol) and then $BF_3{\cdot}Et_2O$ (54 μL, 0.43 mmol). The resulting mixture was allowed to warm to 0 °C in 2 h and, after 1 h, was then warmed to 10 °C. After 1 h the reaction was quenched with 1 N HCl (5 mL) and the mixture was stirred overnight. The organic phase was separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were dried over sodium sulfate. After filtration and evaporation of the solvent, the crude oil was chromatographed (EtOAc−petroleum ether 1:3) to give a mixture of open chain compounds **29** (36 mg, $R_f = 0.44$) as an oil and pure compound **28** (18 mg, 16%, $R_f = 0.25$) as a white solid.

28. Mp 69−70 °C. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.78 (d, $J = 8.4$ Hz, 2 H), 7.29 (d, $J = 8.4$ Hz, 2 H), 4.13 (d, $J = 8.4$ Hz, 1 H), 3.46 (m, 1 H), 3.20 (m, 1 H), 2.52 (dd, $J = 20.5$, 10.3 Hz, 1 H), 2.40 (s, 3 H), 2.40 (m, 1 H), 1.95 (m, 1 H + 1 H), 1.78 (m, 1 H), 1.60 (m, 1 H), 1.10 (d, $J = 6.3$ Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 212.5 (s), 143.4 (s), 129.5 (d, 2 C), 127.6 (d, 2 C), 65.8 (d), 48.6 (t), 47.8 (t), 44.1 (d), 32.2 (d), 30.0 (t), 21.6 (q), 21.1 (q). MS *m*/*z*: 293 (M^+, 5), 222 (100), 155 (90). Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.77. Found: C, 61.14; H, 6.49; N, 5.00.

29. This was obtained as a mixture of two compounds. ^1H NMR (200 MHZ, $CDCl_3$, attributable signals, δ): 7.80−7.60 (m, 2 H + 2 H), 7.40−7.20 (m, 2 H + 2 H), 5.98 (t, $J = 2.6$ Hz, 1 H), 4.03 (t, $J = 7.3$ Hz, 1 H), 3.84 (t, $J = 8.4$ Hz, 1 H), 3.44 (m, 1 H), 3.25 (m, 1 H), 2.84−2.75 (m, 2 H), 2.62−2.43 (m, 1 H), 2.41 (s, 3 H + 3 H), 2.03−1.45 (m, 4 H + 2 H), 1.00−1.79 (m, 3 H + 3 H).

Phosphoric Acid Diphenyl Ester 4,5,6,7-Tetrahydro-oxepin-2-yl Ester (33). This compound was prepared as described for **16** starting from **31** (570 mg, 5 mmol). After chromatography (Et_2O−petroleum ether 1:1, 0.5% Et_3N, $R_f = 0.53$) phosphate **33** (1.47 g, 85%) was obtained as a pale yellow oil. ^1H NMR (200 MHz, $CDCl_3$, δ): 7.40−7.10 (m, 10 H), 4.70 (m, 1 H), 4.25−4.10 (m, 2 H), 1.90−1.50 (m, 6 H). ^{13}C NMR

($CDCl_3$, δ): 173.2 (s), 152.9 (s, 2 C), 130.3 (d, 4 C), 125.7 (d, 2 C), 120.5 (d, 4 C), 89.1 (d), 64.8 (t), 34.5 (t), 22.5 (t), 20.1 (t). MS *m*/*z*: 346 (M^+, 12), 251 (39), 249 (22), 170 (16), 94 (38), 77 (29), 55 (100).

(*E*)-7-(1-Ethoxybuta-1,3-dienyl)-2,3,4,5-tetrahydro-oxepine (35). This compound was prepared as described for **18** starting from **33** (170 mg, 0.5 mmol) and dienylboronate **12a** (105 mg, 0.5 mmol). After purification by flash chromatography (Et_2O−petroleum ether 1:9, 0.5% Et_3N, $R_f = 0.85$) pure **35** (81 mg, 84%) was obtained as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.79 (dt, J = 16.0, 10.0 Hz, 1 H), 5.50−5.40 (m, 2 H), 5.03 (dd, J = 16.0, 1.0 Hz, 1 H), 4.83 (dd, J = 10.0, 1.0 Hz, 1 H), 3.98 (t, J = 6.3, 2 H), 3.77 (q, J = 7.3 Hz, 2 H), 2.30−2.17 (m, 2 H), 1.90−1.80 (m, 2 H), 1.70−1.60 (m, 2 H), 1.30 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 154.7 (s), 154.0 (s), 134.2 (d), 115.0 (d), 113.4 (t), 106.5 (d), 73.4 (t), 64.2 (t), 32.9 (t), 27.1 (t), 25.4 (t), 15.4 (q). MS *m*/*z*: 194 (M^+, 100), 166 (21), 110 (23), 95 (35). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.43; H, 9.01.

6-Methyl-2,3,4,5,6,7-hexahydro-cyclopenta[*b*]oxepin-8-one (37). This compound was prepared as described for **19** starting from **35** (81 mg, 0.42 mmol). Purification by flash chromatography (Et_2O−petroleum ether 1:1, 0.5% Et_3N) gave pure **37** (42 mg, 60%, $R_f = 0.35$) and **39** (6 mg, 9%, $R_f = 0.55$).

37. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 4.00−3.85 (m, 2 H), 2.69−2.55 (m, 3 H), 2.50 (m, 1 H), 2.34 (dt, J = 18.1, 6.5 Hz, 1 H), 1.90−1.76 (m, 2 H), 1.74−1.45 (m, 2 H), 1.01 (d, J = 6.85 Hz, 3 H). ^{13}C NMR (50.33 MHz,$CDCl_3$, δ): 202.8 (s), 157.2 (s), 154.4 (s), 73.8 (t), 42.0 (t), 33.9 (t), 32.9 (d), 30.1 (t), 26.3 (t), 20.5 (q). MS *m*/*z*: 166 (M^+, 100), 67 (85). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.44; H, 8.21.

39. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 6.94 (dq, J = 16.0, 7.3 Hz, 1 H), 6.65 (d, J = 16.0 Hz, 1 H), 6.25 (t, J = 6.3 Hz, 1 H), 3.95 (t, J = 6.5 Hz, 2 H), 2.30−2.15 (m, 2 H), 1.85 (d, J = 7.3 Hz, 3 H), 1.70−1.60 (m, 2 H), 1.19−1.05 (m, 2 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 182.7 (s), 157.3 (s), 144.7 (d), 126.6 (d), 118.7 (d), 73.3 (t), 32.5 (t), 27.3 (t), 25.6 (t), 18.5 (q). MS *m*/*z*: 166 (M^+, 23), 69 (100).

2-Methyl-6-oxo-piperidine-1-carboxylic Acid Benzyl Ester (40). To a stirred suspension of anhydrous K_2CO_3 (3.109 g, 22.5 mmol) in 40 mL of THF were added, under nitrogen atmosphere, 2-methylpiperidine (744 mg, 7.5 mmol) and, dropwise, CbzCl (1.586 g, 9.3 mmol). After 1.5 h the reaction was complete (by TLC); 9 mL of water was added, and the mixture was stirred for 1 h. Afterward, water was added (110 mL) and the mixture extracted with EtOAc (3 × 110 mL). The combined organic layers were washed with a saturated Na_2CO_3 solution (115 mL) and brine (2 × 90 mL) and dried over sodium sulfate. After evaporation of the solvent the *N*-Cbz derivative was obtained as an oil (containing a small amount of unreacted CbzCl) which was directly used in the next oxidation step without further purification. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.33 (m, 5 H), 5.10 (s, 2 H), 4.45 (m, 1 H), 4.00 (m, 1 H), 2.87 (td, J = 13.2, 2.6 Hz, 1 H), 1.68−1.30 (m, 6 H), 1.14 (d, J = 7.0 Hz, 3 H).

$NaIO_4$ (8.02 g, 37.5 mmol) was dissolved in water (55 mL) and $RuO_2 \cdot xH_2O$ (300 mg, 2.25 mmol) was added, under nitrogen atmosphere, to the solution which rapidly turned yellow while being stirred (IMPORTANT: hydrated RuO_2 must be used, because the anhydrous oxide is insoluble). Then a solution of *N*-Cbz 2-methylpiperidine (∼7.5 mmol) in EtOAc (90 mL) was added, the reaction mixture was stirred at room temperature, and the course of reaction was monitored by TLC. After 2 h the reaction was complete, and the two phases were separated. The aqueous layer was extracted with EtOAc (2 × 100 mL), and the combined organic layers were dried over sodium sulfate. After filtration and evaporation of the solvent the crude oil was chromatographed (EtOAc−petroleum ether 2:5, $R_f = 0.36$) to give pure **40** (853 mg, 46%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.45−7.28 (m, 5 H), 5.26 (s, 2 H), 4.40 (m, 1 H), 2.51 (m, 2 H), 2.00−1.60 (m, 4 H), 1.26 (d, J = 6.6 Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 171.3 (s), 154.2 (s), 135.3 (s), 128.4 (d, 2 C), 128.1 (d), 127.9 (d, 2 C), 68.3 (t), 52.0 (d), 34.3 (t), 28.9 (t), 20.2 (q), 16.9 (t). MS *m*/*z*: 247 (M^+, 1), 91 (100). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.17; H, 6.71; N, 5.27.

6-Methyl-1-(toluene-4-sulfonyl)-piperidin-2-one (41). To a stirred solution of 2-methylpiperidine (422 mg, 4.25 mmol) in anhydrous pyridine (15 mL), under nitrogen atmosphere, was added DMAP (52 mg, 0.42 mmol) followed by TsCl (1.013 g, 5.31 mmol). The solution was stirred at room temperature overnight and then concentrated under vacuum. The residue was dissolved in CH_2Cl_2 (25 mL) and washed with a 1 M solution of citric acid (3 × 25 mL). The organic layer was dried over sodium sulfate and concentrated to give the *N*-Ts 2-methylpiperidine as an oil (containing a small amount of unreacted TsCl) which was directly used in the next oxidation step without further purification. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.68 (d, J = 8.1 Hz, 2 H), 7.26 (d, J = 8.1 Hz, 2 H), 4.20 (m, 1 H), 3.68 (br d, J = 13.5 Hz, 1 H), 2.95 (t, J = 13.5 Hz, 1 H), 2.39 (s, 3 H), 1.65−1.35 (m, 6 H), 1.04 (d, J = 7.0 Hz, 3 H).

The oxidation of crude *N*-Ts 2-methylpiperidine (∼4.25 mmol) was carried out as described above for the synthesis of **40**, yielding after chromatography (EtOAc−petroleum ether 1:2, $R_f = 0.34$) pure **41** (574 mg, 43%) as a white solid: mp 108−110 °C. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.89 (d, J = 8.4 Hz, 2 H), 7.27 (d, J = 8.4 Hz, 2 H), 4.75 (m, 1 H), 2.40 (s, 3 H), 2.45−2.35 (m, 2 H), 2.00−1.65 (m, 4 H), 1.45 (d, J = 6.6 Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 169.9 (s), 144.3 (s), 136.6 (s), 129.0 (d, 2 C), 128.7 (d, 2 C), 52.6 (d), 33.3 (t), 29.7 (t), 21.5 (q, 2 C), 16.0 (t). MS *m*/*z*: 267 (M^+, 1), 188 (84), 108 (96), 91 (100). Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.40; H, 6.41; N, 5.24. Found: C, 58.55; H, 6.39; N, 4.98.

2-Methyl-6-trifluoromethanesulfonyloxy-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Benzyl Ester (42). To a solution of **40** (565 mg, 2.28 mmol) in THF (12.5 mL) cooled to −70 °C was added dropwise a 1 M solution of LHMDS in THF (2.85 mL, 2.85 mmol) in about 30 min, and the resulting mixture was stirred for 70 min. HMPA (0.80 mL, 4.60 mmol) was then added followed, after 15 min, by a solution of $PhNTf_2$ (1.018 g, 2.28 mmol) in THF (2.5 mL). The reaction mixture was then allowed to warm to room temperature and stirred overnight. Then water (23 mL) was added and the mixture was extracted with Et_2O (3 × 18 mL). The combined organic layers were washed with 10% NaOH (3 × 18 mL) and dried over sodium sulfate. After evaporation the crude reaction mixture was chromatographed (EtOAc−petroleum ether 1:10, 0.5% Et_3N, $R_f = 0.49$) to give **42** (529 mg) in 61% yield as a whitish solid: mp 33−34 °C. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.45 (m, 5 H), 5.30 (t, J = 3.7 Hz, 1 H), 5.19 (AB system, J = 12.5 Hz, 2 H), 4.70 (m, 1 H), 2.32−2.10 (m, 2 H), 1.80−1.56 (m, 2 H), 1.16 (d, J = 7.0 Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 153.8 (s), 137.7 (s), 135.3 (s), 128.4 (d, 2 C), 128.3 (d), 128.2 (d, 2 C), 118.3 (q, J_{C-F} = 320 Hz), 106.4 (d), 68.4 (t), 50.4 (d), 26.7 (t), 18.8 (t), 15.2 (q). MS *m*/*z*: 91 (100).

Trifluoromethanesulfonic Acid 6-Methyl-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydropyridin-2-yl Ester (43). This compound was prepared as reported above for **42**. Starting from **41** (478 mg, 1.79 mmol), **43** (381 mg) was obtained after chromatography (EtOAc−petroleum ether 1:8, $R_f = 0.27$) in 53% yield as a white solid: mp 49−51 °C. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.73 (d, J = 8.1 Hz, 2 H), 7.31 (d, J = 8.1 Hz, 2 H), 5.41 (t, J = 3.67 Hz, 1 H), 4.40 (m, 1 H), 2.43 (s, 3 H), 2.10−2.00 (m, 2 H), 1.40−1.15 (m, 2 H), 1.14 (d, J = 7.0 Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 144.6 (s), 138.7 (s), 136.7 (s), 129.7 (d, 2 C), 127.7 (d, 2 C), 118.3 (q, J_{C-F} = 321 Hz), 108.9 (d), 52.9 (d), 24.0 (t), 21.6 (q), 18.6 (t), 16.0 (q). MS *m*/*z*: 399 (M^+, 1), 155 (55), 91 (100).

6-(1-Ethoxybuta-1,3-dienyl)-2-methyl-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Benzyl Ester (44). To a solution of **42** (190 mg, 0.5 mmol) and boronate **12a** (315 mg, 1.50 mmol) in THF (7 mL) were added, under a nitrogen atmosphere, $(Ph_3P)_2PdCl_2$ (18 mg, 0.025 mmol) and a 2 M aqueous Na_2CO_3 solution (4.5 mL). The mixture was stirred for 4 h at

60 °C. Water (14 mL) was then added and the mixture was extracted with diethyl ether (3 × 20 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded a yellow oil which was purified by chromatography (EtOAc−petroleum ether 1:15, 1% Et_3N, $R_f = 0.37$) to give **44** (104 mg, 63%) as a colorless oil. ^1H NMR (200 MHz, $CDCl_3$, δ): 7.28 (m, 5 H), 6.61 (ddd, $J = 16.9, 10.6, 10.3$ Hz, 1), 5.28 (t, $J = 3.3$ Hz, 1 H), 5.21 (d, $J = 10.6$ Hz, 1 H), 5.07 (s, 2 H), 4.87 (dd, $J = 16.9, 2.2$ Hz, 1 H), 4.74 (dd, $J = 10.3, 2.2$. Hz, 1 H), 4.65 (m, 1 H), 3.60−3.40 (m, 2 H), 2.22−2.10 (m, 2 H), 1.85 (m, 1 H), 1.61 (m 1 H), 1.15 (d, $J = 6.9$ Hz, 3 H), 1.13 (m, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 156.4 (s), 136.2 (s), 133.8 (d), 131.6 (s), 128.2 (d, 2 C), 127.9 (d, 2 C), 127.8 (d), 117.5 (d), 110.8 (t), 67.3 (t), 63.1 (t), 47.2 (d), 27.5 (t), 19.2 (t), 15.9 (q), 15.7 (q). MS *m/z*: 327 (M^+, 4), 91 (100). Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.66; H, 7.38; N, 4.12.

6-(1-Ethoxybuta-1,3-dienyl)-2-methyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydropyridine (45). This compound was prepared as reported above for **44**. Starting from **43** (299 mg, 0.75 mmol), pure **45** (168 mg) was obtained after chromatography (EtOAc−petroleum ether 1:15, 0.5% Et_3N, $R_f = 0.30$) in 64% yield as a colorless oil. ^1H NMR (200 MHz, $CDCl_3$, δ): 7.70 (d, $J = 8.4$ Hz, 2 H), 7.25 (d, $J = 8.4$ Hz, 2 H), 6.60 (ddd, $J = 16.8, 10.6, 10.2$ Hz, 1 H), 5.50−5.40 (m, 1 H + 1 H), 5.02 (d, $J = 16.8$ Hz, 1 H), 4.80 (d, $J = 10.2$ Hz, 1 H), 4.27 (m, 1 H), 3.77 (dq, $J = 22.3, 7.0$ Hz, 2 H), 2.40 (s, 3 H), 2.03−1.96 (m, 2 H), 1.27 (t, $J = 6.9$ Hz, 3 H), 1.40−1.03 (m, 2 H), 1.13 (d, $J = 6.9$ Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, attributable signals, δ): 143.1 (s), 136.6 (s), 133.9 (d), 129.3 (d, 2 C), 127.6 (d, 2 C), 120.6 (d), 111.4 (t), 104.9 (d), 63.6 (t), 49.5 (d), 24.8 (t), 21.5 (q), 18.8 8t), 16.8 (q), 14.6 (q). MS *m/z*: 347 (M^+, 0.5), 91 (100). Anal. Calcd for $C_{19}H_{25}NO_3S$: C, 65.68; H, 7.25; N, 4.03. Found: C, 65.79; H, 7.02; N, 3.78.

(2*S,5*S**)-2,5-Dimethyl-7-oxo-2,3,4,5,6,7-hexahydro[1]-pyrindine-1-carboxylic Acid Benzyl Ester (46).** To a solution of **44** (104 mg, 0.32 mmol) in $CHCl_3$ (4 mL) was added Amberlyst 15 (60 mg), and the resulting mixture was stirred at room temperature and monitored by TLC. After 18 h the mixture was filtered through a short pad of $NaHCO_3$ and concentrated. The residue was chromatographed (EtOAc−petroleum ether 1:5, 0.5% Et_3N, $R_f = 0.15$) to give pure **46** (64 mg, 67%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.30 (m, 5 H), 5.15 (AB system, $J = 12.5$ Hz, 2 H), 4.61 (m, 1 H), 2.75 (m, 1 H), 2.72 (dd, $J = 18.5, 6.6$ Hz, 1 H), 2.45 (ddd, $J = 19.4, 11.4, 7.3$ Hz, 1 H), 2.19 (dd, $J = 19.4, 5.9$ Hz, 1 H), 1.99 (d, $J = 18.5$ Hz, 1 H), 1.90 (m, 1 H), 1.76 (m, 1 H), 1.16 (d, $J = 7.0$ Hz, 3 H), 1.02 (d, $J = 6.9$ Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 199.6 (s), 160.1 (s), 153.7 (s), 136.2 (s), 135.2 (s), 128.3 (d, 2 C), 128.1 (d, 2 C), 127.9 (d), 67.9 (t), 47.9 (d), 42.6 (t), 33.2 (d), 26.6 (t), 20.3 (t), 19.2 (q), 16.0 (q). MS *m/z*: 299 (M^+, 6), 240 (80), 91 (100). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.05; H, 7.18; N, 4.71.

(2*S,5*S**)-2,5-Dimethyl-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro[1]pyrindin-7-one (47).** The hydrolysis of **43** (138 mg, 0.40 mmol) was performed as described above for the synthesis of **46**. Chromatography (EtOAc−petroleum ether 1:4, 0.5% Et_3N, $R_f = 0.23$) gave the Nazarov product **47** (72 mg, 57%) as a white solid: mp 142−143 °C. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.98 (d, $J = 8.4$ Hz, 2 H), 7.28 (d, $J = 8.4$ Hz, 2 H), 4.32 (m, 1 H), 2.81 (m, 1 H), 2.75 (dd, $J = 18.7, 6.6$ Hz, 1 H), 2.39 (s, 3 H), 2.39 (m, 1 H), 2.30 (dd, $J = 19.4, 5.9$ Hz, 1 H), 2.14 (m, 1 H), 1.97 (d, $J = 18.7$ Hz, 1 H), 1.77 (m, 1 H), 1.15 (d, $J = 7.0$ Hz, 3 H), 0.85 (d, $J = 7.0$ Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, attributable signals, δ): 162.3 (s), 143.3 (s), 138.1 (s), 134.2 (s), 129.2 (d, 2 C), 127.7 (d, 2 C), 49.9 (d), 42.2 (t), 33.7 (d), 25.9 (t), 21.4 (q), 19.9 (t), 19.3 (q), 16.4 (q). MS *m/z*: 319 (M^+, 47), 91 (100). Anal. Calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39. Found: C, 63.77; H, 6.82; N, 4.01.

5-Methyl-2-oxo-piperidine-1-carboxylic Acid Benzyl Ester (53). The procedure reported for the synthesis of **40** was used starting from 3-methylpiperidine (590 mg, 5.95 mmol). After formation of the *N*-Cbz derivative [^1H NMR ($CDCl_3$, δ) 7.33 (m, 5 H), 5.10 (s, 2 H), 4.15−3.90 (m, 2 H), 2.74 (td, $J = 13.2, 3.3$ Hz, 1 H), 2.40 (m, 1 H), 1.85−1.35 (m, 4 H), 1.05 (m, 1 H), 0.86 (d, $J = 6.6$ Hz, 3 H)] and oxidation, chromatography (EtOAc−petroleum ether 1:3.5) gave pure **53** (270 mg, 18%, $R_f = 0.32$) and its 3-methyl isomer (109 mg, 7%, $R_f = 0.45$), both as a colorless oils.

53. ^1H NMR (200 MHz, $CDCl_3$, δ): 7.50−7.20 (m, 5 H), 5.26 (s, 2 H), 3.88 (dd, $J = 12.5, 4.4$ Hz, 1 H), 3.16 (dd, $J = 12.5, 10.6$ Hz, 1 H), 2.60−2.40 (m, 2 H), 2.20−1.80 (m, 2 H), 1.46 (m, 1 H), 1.02 (d, $J = 6.6$ Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 172.0 (s), 154.0 (s), 135.3 (s), 128.6 (d, 2 C), 128.2 (d), 128.0 (d, 2 C), 68.5 (t), 52.9 (t), 34.2 (t), 28.7 (d), 28.6 (t), 18.7 (q). MS *m/z*: 247 (M^+, 1), 113 (95), 91 (100). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.22; H, 6.66; N, 5.32.

4-Methyl-2-oxo-piperidine-1-carboxylic Acid Benzyl Ester (54). The procedure reported for the synthesis of **40** was used starting from 4-methylpiperidine (838 mg, 8.4 mmol). After formation of the *N*-Cbz derivative [^1H NMR (200 MHz, $CDCl_3$, δ) 7.32 (m, 5 H), 5.09 (s, 2 H), 4.12 (m, 2 H), 2.73 (t, $J = 12.8$ Hz, 2 H), 1.55 (m, 2 H + 1 H), 1.10 (m, 2 H), 0.91 (d, $J = 6.2$ Hz, 3 H)] and oxidation, chromatography (EtOAc−petroleum ether 1:3, $R_f = 0.29$) gave pure **54** (1.160 g, 56%) as a colorless oil. ^1H NMR (200 MHz, $CDCl_3$, δ): 7.54−7.20 (m, 5 H), 5.26 (s, 2 H), 3.88 (ddd, $J = 12.7, 5.2, 4.4$ Hz, 1 H), 3.55 (ddd, $J = 12.7, 11.0, 4.4$ Hz, 1 H), 2.63 (ddd, $J = 16.3, 4.4, 1.8$ Hz, 1 H), 2.20−1.80 (m, 1 H + 2 H), 1.45 (m, 1 H), 1.01 (d, $J = 6.2$ Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 171.2 (s), 154.2 (s), 135.3 (s), 128.4 (d, 2 C), 128.1 (d), 127.9 (d, 2 C), 68.3 (t), 46.0 (t), 42.9 (t), 30.6 (t), 27.5 (d), 21.0 (q). MS *m/z*: 247 (M^+, 1), 113 (80), 91 (100). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.72; H, 6.80; N, 5.60.

4-Methyl-1-(toluene-4-sulfonyl)-piperidin-2-one (55). This compound was prepared as reported above for **41**. Starting from **51** (1.676 g, 16.9 mmol), the *N*-Ts derivative was obtained as an oil (containing a small amount of unreacted TsCl) and was directly used in the next oxidation step without further purification. ^1H NMR ($CDCl_3$, δ): 7.61 (d, $J = 7.7$ Hz, 2 H), 7.29 (d, $J = 7.7$ Hz, 2 H), 3.73−3.68 (m, 2 H), 2.41 (s, 3 H), 2.19 (t, $J = 11.7$ Hz, 2 H), 1.59−1.61 (m, 2 H), 1.26−1.31 (m, 3 H), 0.88 (d, $J = 4.8$ Hz, 3 H).

The oxidation of crude *N*-Ts 4-methylpiperidine (∼16.9 mmol) was carried out as described above for the synthesis of **40**, yielding after chromatography (EtOAc−petroleum ether 1:8, $R_f = 0.52$) pure **55** (2.304 g, 51% over 2 steps) as a colorless oil. ^1H NMR ($CDCl_3$, δ): 7.88 (d, $J = 8.1$ Hz, 2 H), 7.28 (d, $J = 8.1$ Hz, 2 H), 4.15 (dt, $J = 12.0$ Hz, $J = 4.1$ Hz, 1 H), 3.63 (td, $J = 12.1$ Hz, 4.4 Hz, 1 H), 2.48 (m, 1 H), 2.40 (s, 3 H), 2.15−1.86 (m, 3 H), 1.49 (m, 1 H), 0.97 (d, $J = 6.3$ Hz, 3 H). ^{13}C NMR ($CDCl_3$, δ): 169.9 (s), 144.6 (s), 136.1 (s), 129.2 (d, 2 C), 128.6 (d, 2 C), 45.9 (t), 42.1 (t), 31.0 (t), 27.4 (d), 21.6 (q), 20.6 (q). MS *m/z*: 267 (M^+, 4), 91 (100). Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.40; H, 6.41; N, 5.24. Found: C, 58.26; H, 6.32; N, 5.06.

4-*tert*-Butyl-2-oxo-piperidine-1-carboxylic Acid Benzyl Ester (56). The procedure reported for the synthesis of **40** was used starting from 4-*tert*-butylpiperidine (932 mg, 6.6 mmol). After formation of the *N*-Cbz derivative [^1H NMR (200 MHz, $CDCl_3$, δ) 7.33 (m, 5 H), 5.10 (s, 2 H), 4.20 (m, 2 H), 2.64 (m, 2 H), 1.65 (m, 2 H), 1.08 (m, 2 H + 1 H), 0.82 (s, 9 H)] and oxidation, chromatography (EtOAc−petroleum ether 1:4, $R_f = 0.39$) gave pure **56** (629 mg, 33%) as a colorless oil. ^1H NMR (200 MHz, $CDCl_3$, δ): 7.45−7.25 (m, 5 H), 5.26 (s, 2 H), 3.90 (dt, $J = 12.8, 4.4$ Hz, 1 H), 3.52 (td, $J = 12.8, 4.4$ Hz, 1 H), 2.60 (ddd, $J = 16.8, 5.1, 2.2$ Hz, 1 H), 2.25 (dd, $J = 16.8, 11.4$ Hz, 1 H), 1.92 (m, 1 H), 1.70−1.30 (m, 2 H), 0.86 (m, 9 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 171.7 (s), 153.7 (s), 135.3 (s), 128.4 (d, 2 C), 128.1 (d), 127.9 (d, 2 C), 68.2 (t), 45.9 (t), 42.3 (d), 36.8 (t), 32.1 (s), 26.5 (q, 3 C), 24.2 (t). MS *m/z*: 289 (M^+, 1), 155 (60), 91 (100). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.73; H, 7.85; N, 4.64.

3-Methyl-6-trifluoromethanesulfonyloxy-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Benzyl Ester (57). This compound was prepared as reported above for **42**. Starting from **53** (259 mg, 1.05 mmol), **57** (264 mg) was obtained after chromatography (EtOAc−petroleum ether 1:10, 0.5% Et_3N, R_f = 0.36) in 66% yield as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.35 (m, 5 H), 5.28 (t, J = 4.0 Hz, 1 H), 5.20 (s, 2 H), 3.95 (dd, J = 12.8, 2.9 Hz, 1 H), 3.01 (dd, J = 12.8, 9.5 Hz, 1 H), 2.38 (m, 1 H), 1.90−1.70 (m, 1 H), 1.33 (m, 1 H), 0.95 (d, J = 6.6 Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 153.6 (s), 139.2 (s), 135.3 (s), 128.5 (d, 2 C), 128.4 (d), 128.2 (d, 2 C), 118.4 (q, J_{C-F} = 321 Hz), 107.0 (d), 68.5 (t), 51.9 (t), 30.5 (t), 28.4 (d), 17.9 (q). MS *m*/*z*: 92 (100).

4-Methyl-6-trifluoromethanesulfonyloxy-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Benzyl Ester (58). This compound was prepared as reported above for **42**. Starting from **54** (495 mg, 2.00 mmol), **58** (414 mg) was obtained after chromatography (EtOAc−petroleum ether 1:10, 0.5% Et_3N, R_f = 0.46) in 55% yield as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.34 (m, 5 H), 5.19 (s + d, 2 H + 1 H), 3.75−3.55 (m, 2 H), 2.50 (m, 1 H), 1.86 (m, 1 H), 1.42 (m, 1 H), 1.06 (d, J = 7.0 Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 153.4 (s), 139.2 (s), 135.3 (s), 128.5 (d, 2 C), 128.4 (d), 128.2 (d, 2 C), 118.4 (q, J_{C-F} = 321 Hz), 112.7 (d), 68.5 (t), 44.7 (t), 30.7 (t), 28.3 (d), 20.6 (q). MS *m*/*z*: 90 (100).

Trifluoromethanesulfonic Acid 4-Methyl-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydropyridin-2-yl Ester (59). This compound was prepared as reported above for **42**. Starting from **55** (800 mg, 2.99 mmol), **59** was obtained as a colorless oil which was used in the coupling step without further purification. ^{1}H NMR ($CDCl_3$, δ): 7.75 (d, J = 8.1 Hz, 2 H), 7.33 (d, J = 8.1 Hz, 2 H), 5.31 (d, J = 3.7, 1 H), 3.72 (m, 1 H), 3.54 (m, 1 H), 2.43 (s, 3 H), 2.38−2.28 (m, 2 H), 1.53 (m, 1 H), 0.87 (d, J = 7.3 Hz, 3 H).

4-*tert*-Butyl-6-trifluoromethanesulfonyloxy-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Benzyl Ester (60). This compound was prepared as reported above for **42**. Starting from **56** (629 mg, 2.17 mmol), **60** (547 mg) was obtained after chromatography (EtOAc−petroleum ether 1:20, 0.5% Et_3N, R_f = 0.40) in 60% yield as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.34 (m, 5 H), 5.33 (d, J = 3.7 Hz, 1 H), 5.19 (AB system, J = 12.5 Hz, 2 H), 4.30 (m, 1 H), 3.15 (td, J = 12.0, 2.2 Hz, 1 H), 2.24 (m, 1 H), 1.81 (m, 1 H), 1.52 (m, 1 H), 0.87 (s, 9 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 153.8 (s), 140.4 (s), 135.4 (s), 128.4 (d, 2 C), 128.3 (d), 128.0 (d, 2 C), 118.3 (q, J_{C-F} = 321 Hz), 109.5 (d), 68.3 (t), 46.7 (t), 44.7 (d), 33.2 (s), 27.0 (q, 3 C), 25.1 (t). MS *m*/*z*: 91 (100).

6-(1-Ethoxybuta-1,3-dienyl)-3-methyl-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Benzyl Ester (61). This compound was prepared as reported above for **44**, but the reaction was stirred for 4.5 h. Starting from **57** (128 mg, 0.34 mmol), pure **61** (68 mg) was obtained after chromatography (EtOAc−petroleum ether 1:15, 1% Et_3N, R_f = 0.43) in 61% yield as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.29 (m, 5 H), 6.52 (ddd, J = 17.2, 10.6, 10.6 Hz, 1), 5.28 (t, J = 3.6 Hz, 1 H), 5.12 (d, J = 10.6 Hz, 1 H), 5.08 (s, 2 H), 4.95 (dd, J = 17.2, 1.8 Hz, 1 H), 4.75 (dd, J = 10.6, 1.8 Hz, 1 H), 4.00 (dd, J = 12.7, 2.5 1 H), 3.90−3.40 (m, 2 H), 2.97 (dd, J = 12.7, 9.8 Hz, 1 H), 2.30 (m, 1 H), 1.85−1.64 (m, 2 H), 1.10−1.00 (m, 3 H), 0.98 (d, J = 6.2 Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 155.9 (s), 143.5 (s), 136.1 (s), 133.7 (d), 132.7 (s), 128.2 (d, 2 C), 128.0 (d, 2 C), 127.8 (d), 118.3 (d), 111.1 (t), 103.7 (d), 67.4 (t), 63.2 (t), 50.1 (t), 31.6 (t), 28.5 (d), 18.5 (q), 14.5 (q). MS *m*/*z*: 327 (M^+, 6), 91 (100). Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.54; H, 7.41; N, 4.09.

6-(1-Ethoxybuta-1,3-dienyl)-4-methyl-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Benzyl Ester (62). This compound was prepared as reported above for **44**, but the reaction was stirred for 6.5 h. Starting from **58** (190 mg, 0.50 mmol), pure **62** (103 mg) was obtained after chromatography (EtOAc−petroleum ether 1:15, 1% Et_3N, R_f = 0.36) in 63% yield as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.29 (m, 5 H), 6.55 (ddd, J = 16.8, 10.6, 9.9 Hz, 1), 5.24 (d, J = 10.6 Hz, 1 H), 5.18 (d, J = 3.3 Hz, 1 H), 5.08 (s, 2 H), 4.96 (dd, J = 16.8, 1.8 Hz, 1 H), 4.76 (dd, J = 9.9, 1.8. Hz, 1 H), 3.80−3.40 (m, 2 H + 2 H), 2.40 (m, 1 H), 1.91 (m, 1 H), 1.48 (m 1 H), 1.10−1.00 (m, 3 H), 1.05 (d, J = 6.9 Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 155.9 (s), 152.7 (s), 136.1 (s), 133.8 (d), 131.9 (s), 128.1 (d, 2 C), 128.0 (d, 2 C), 127.9 (d), 124.2 (d), 111.1 (t), 103.8 (d), 67.4 (t), 63.2 (t), 42.6 (t), 31.2 (t), 28.4 (d), 21.0 (q), 14.5 (q). MS *m*/*z*: 327 (M^+, 5), 91 (100). Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.39; H, 7.55; N, 4.17.

6-(1-Ethoxybuta-1,3-dienyl)-4-methyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydropyridine (63). This compound was prepared as reported above for **44**. Starting from **59** (170 mg, 0.42 mmol), pure **63** (98 mg) was obtained after chromatography (EtOAc−petroleum ether 1:15, 0.5% Et_3N, R_f = 0.21) in 67% yield as a colorless oil. ^{1}H NMR ($CDCl_3$, δ): 7.69 (d, J = 8.4 Hz, 2 H), 7.26 (d, J = 8.4 Hz, 2 H), 6.53 (ddd, J = 16.9, 10.6, 10.3 Hz, 1 H), 5.46 (d, J = 10.6 Hz, 1 H), 5.33 (d, J = 3.3 Hz, 1 H), 5.04 (dd, J = 16.9, 1.8 Hz, 1 H), 4.81 (dd, J = 10.3, 1.8 Hz, 1 H), 3.77 (q, J = 6.6 Hz, 2 H), 3.63−3.44 (m, 2 H), 2.40 (s, 3 H), 2.28−2.15 (m, 1 H), 1.58−1.48 (m, 1 H), 1.15−1.05 (m, 3 H), 0.86 (d, J = 7.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$, δ): 155.8 (s), 143.3 (s), 136.8 (s), 133.8 (d), 131.2 (s), 129.3 (d, 2 C), 127.7 (d, 2 C), 127.4 (d), 111.9 (t), 105.4 (d), 63.7 (t), 44.8 (t), 28.9 (t), 28.0 (d), 21.5 (q), 20.7 (q), 14.6 (q). MS *m*/*z*: 347 (M^+, 1.5), 91 (100). Anal. Calcd for $C_{19}H_{25}NO_3S$: C, 65.68; H, 7.25; N, 4.03. Found: C, 65.77; H, 6.98; N, 3.91.

4-*tert*-Butyl-6-(1-ethoxybuta-1,3-dienyl)-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Benzyl Ester (64). This compound was prepared as reported above for **44**. Starting from **60** (211 mg, 0.50 mmol), pure **64** (80 mg) was obtained after chromatography (EtOAc−petroleum ether 1:30, 1% Et_3N, R_f = 0.23) in 43% yield as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.28 (m, 5 H), 6.60 (ddd, J = 17.2, 10.6, 10.3 Hz, 1 H), 5.30 (d, J = 3.3 Hz, 1 H), 5.27 (d, J = 10.6 Hz, 1 H), 5.08 (s, 2 H), 4.97 (dd, J = 17.2, 1.8 Hz, 1 H), 4.74 (dd, J = 10.3, 1.8. Hz, 1 H), 4.24 (dt, J = 12.8, 3.7 Hz, 1 H), 3.80−3.30 (m, 2 H), 3.16 (td, J = 12.8, 2.6 Hz, 1 H), 2.13 (m, 1 H), 1.82 (m, 1 H), 1.60 (m 1 H), 1.10 (t, J = 7.0 Hz, 3 H), 0.91 (s, 9 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 156.5 (s), 136.2 (s), 133.9 (d), 133.6 (s), 128.1 (d, 2 C), 128.0 (d, 2 C), 127.9 (d), 120.9 (d), 111.1 (t), 104.1 (d), 67.2 (t), 63.3 (t), 45.1 (d), 44.6 (t), 33.2 (s), 27.3 (q, 3 C), 25.6 (t), 14.6 (q). MS *m*/*z*: 369 (M^+, 9), 91 (100). Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46; N, 3.79. Found: C, 74.91; H, 8.13; N, 3.55.

3,5-Dimethyl-7-oxo-2,3,4,5,6,7-hexahydro-[1]pyrindine-1-carboxylic Acid Benzyl Ester (65). This was obtained as a diastereomeric mixture. The hydrolysis of **61** (63 mg, 0.19 mmol) was carried out as described above. Chromatography (EtOAc−petroleum ether 1:3.5, 0.5% Et_3N, R_f = 0.23) gave **65** (32 mg, 56%) as a ∼1.2:1 mixture of inseparable diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.40−7.22 (m, 5 H + 5 H), 5.18 (AB system, J = 12.3 Hz, 2 H + 2 H), 3.90 (m, 1 H + 1 H), 3.00−2.90 (m, 1 H + 1 H), 2.78−2.69 (m, 2 H + 1 H), 2.63 (dd, J = 20.1, 6.4 Hz, 1 H), 2.35 (m, 1 H), 2.23−1.98 (m, 2 H + 2 H), 1.84 (dd, J = 19.7, 7.9 Hz, 1 H), 1.21 (d, J = 5.7 Hz, 3 H), 1.19 (d, J = 5.7 Hz, 3 H), 1.02 (d, J = 6.6 Hz, 3 H + 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, assigned peaks, δ): 128.3 (d, 2 C, both diastereomers), 128.1 (d, 2 C, both diastereomers), 127.9 (d, both diastereomers), 67.9 (t, both diastereomers), 50.4 and 50.3 (t), 43.1 and 42.9 (t), 33.1 (d, both diastereomers), 32.4 and 32.3 (t), 28.1 and 27.9 (d), 19.1 and 18.9 (q), 18.3 (q, both diastereomers). MS *m*/*z*: 299 (M^+, 1), 91 (100).

(4*R,5*S**)-4,5-Dimethyl-7-oxo-2,3,4,5,6,7-hexahydro[1]-pyrindine-1-carboxylic Acid Benzyl Ester (66).** The hydrolysis of **62** (103 mg, 0.32 mmol) was carried out as described above. Chromatography (EtOAc−petroleum ether 1:5, 0.5% Et_3N) gave dienone **70** (14 mg, 15%, R_f = 0.38) and **66** (44 mg, 46%, R_f = 0.16) both as yellowish oils.

66. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.33 (m, 5 H), 5.15 (s, 2 H), 3.68 (ddd, J = 16.1, 7.0, 2.9 Hz, 1 H), 3.46 (ddd, J = 16.1, 8.8, 2.9 Hz, 1 H), 2.86 (m, 1 H), 2.65 (dd, J = 19.0, 6.6 Hz, 1

H), 2.61 (m, 1 H), 2.00 (d, J = 19.0 Hz, 1 H), 1.96 (m, 1 H), 1.56 (m, 1 H), 1.14 (d, J = 6.2 Hz, 3 H), 1.11 (d, J = 6.2 Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 191.1 (s), 164.6 (s), 153.9 (s), 137.0 (s), 136.1 (s), 128.3 (d, 2 C), 128.0 (d, 2 C), 127.9 (d), 68.0 (t), 42.8 (t), 42.6 (t), 31.0 (t), 30.8 (d), 28.4 (d), 18.8 (q), 18.0 (q). MS m/z: 299 (M^+, 6), 240 (100). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.17; H, 7.33; N, 4.87.

70. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.28 (m, 5 H), 6.80 (dq, J = 15.8, 6.6 Hz, 1 H), 6.19 (d, J = 15.8 Hz, 1 H), 5.68 (d, J = 3.3 Hz, 1 H), 5.07 (s, 2 H), 3.80−3.50 (m, 2 H), 2.40 (m, 1 H), 1.91 (m, 1 H), 1.76 (d, J = 6.6 Hz, 3 H), 1.49 (m, 1 H), 1.02 (d, J = 6.9 Hz, 3 H).

(4*R,5*S**)-4,5-Dimethyl-1-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro[1]pyrindin-7-one (67).** The hydrolysis of **63** (50 mg, 0.14 mmol) was carried out as described above for the synthesis of **46**. After 24 h, chromatography (EtOAc−petroleum ether 1:4, 0.5% Et_3N, R_f = 0.23) gave the Nazarov product **67** (23 mg, 51%) as a white solid and dienone **71** (6 mg, 7%, R_f = 0.39).

67. Mp 113−114 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.97 (d, J = 8.4 Hz, 2 H), 7.28 (d, J = 8.4 Hz, 2 H), 3.53 (m, 1 H), 3.29 (m, 1 H), 2.91 (m, 1 H), 2.74−2.53 (m, 2 H), 2.39 (s, 3 H), 2.13−1.96 (m, 2 H), 1.67 (m, 1 H), 1.15 (d, J = 6.2 Hz, 3 H), 1.11 (d, J = 6.9 Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 190.0 (s), 166.2 (s), 143.4 (s), 138.2 (s), 136.2 (s), 129.3 (d, 2 C), 127.8 (d, 2 C), 44.7 (t), 42.2 (t), 31.3 (d), 30.6 (t), 28.1 (d), 21.5 (q), 19.0 (q), 17.8 (q). MS m/z: 319 (M^+, 44), 91 (100). Anal. Calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39. Found: C, 63.81; H, 6.94; N, 4.12.

71. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.71 (d, J = 8.4 Hz, 2 H), 7.29 (d, J = 8.4 Hz, 2 H), 6.99 (dq, J = 15.7 Hz, 7.0 Hz, 1 H), 6.57 (d, J = 15.7 Hz, 1 H), 5.91 (d, J = 3.3 Hz, 1 H), 3.60−3.32 (m, 2 H), 2.40 (s, 3 H), 2.21 (m, 1 H), 1.93 (d, J = 7.0 Hz, 3 H), 1.47−1.36 (m, 2 H), 1.21 (d, J = 8.8 Hz, 3 H).

6-But-2-enoyl-4-*tert*-butyl-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Benzyl Ester (72). The hydrolysis of **64** (80 mg, 0.22 mmol) was carried out as described above. Chromatography (EtOAc−petroleum ether 1:10, 0.5% Et_3N, R_f = 0.38) gave dienone **72** (34 mg) in 45% yield as a yellowish oil. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.28 (m, 5 H), 6.80 (dq, J = 15.4, 6.7 Hz, 1 H), 6.19 (d, J = 15.4 Hz, 1 H), 5.83 (d, J = 2.9 Hz, 1 H), 5.07 (s, 2 H), 4.15 (dt, J = 12.8, 3.7 Hz, 1 H), 3.20 (td, J = 12.8, 2.9 Hz, 1 H), 2.10 (m, 1 H), 1.84 (m, 1 H), 1.78 (d, J = 6.7 Hz, 3 H), 1.60 (m, 1 H), 0.91 (s, 9 H). ^{13}C NMR ($CDCl_3$, δ): 197.9 (s), 155.9 (s), 143.4 (d), 139.9 (s), 135.7 (s), 128.5 (d), 128.3 (d, 2 C), 128.2 (d, 2 C), 128.1 (d), 123.1 (d), 67.8 (t), 44.7 (d), 44.3 (t), 33.2 (s), 27.3 (q, 3 C), 25.2 (t), 18.2 (q). MS m/z: 341 (M^+, 2), 91 (100). Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.65; H, 8.12; N, 4.43.

Phosphoric Acid 5-Ethyl-4,5,6,7-tetrahydro-oxepin-2-yl Ester Diphenyl Ester (73). This compound was prepared as described for **16** starting from 5-ethyl-oxepan-2-one (710 mg, 5 mmol). After chromatography (Et_2O−petroleum ether 1:1, 0.5% Et_3N, R_f = 0.53) phosphate **73** (1.27 g, 68%) was obtained as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.40−7.10 (m, 10 H), 4.70 (m, 1 H), 4.30−3.85 (m, 2 H), 2.10−1.80 (m, 3 H), 1.45 (m, 1H), 1.35−1.20 (m, 3 H), 0.92 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 172.3 (s), 157.7 (s, 2 C), 129.6 (d, 4 C), 121.3 (d, 2 C), 116.3 (d, 4 C), 89.9 (d), 65.7 (t), 37.9 (t), 33.5 (d), 27.6 (t), 23.5 (t), 11.9 (q).

(*E*)-7-(1-Ethoxybuta-1,3-dienyl)-4-ethyl-2,3,4,5-tetrahydro-oxepine (74). This compound was prepared as described for **18** starting from **73** (190 mg, 0.5 mmol) and α-ethoxydienylboronate **12a** (105 mg, 0.5 mmol). After purification by flash chromatography (Et_2O−petroleum ether, 1:9, 0.5% Et_3N, R_f = 0.78) pure **74** (84 mg, 76%) was obtained as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 6.81 (dt, J = 16.0, 10.0 Hz, 1 H), 5.43 (m, 1 H), 5.22 (d, J = 10.0 Hz, 1 H), 5.02 (dd, J = 16.0, 1.0 Hz, 1 H), 4.83 (dd, J = 10.0, 1.0 Hz, 1 H), 3.90−3.75 (m, 2 H), 3.47 (q, J = 7.3 Hz, 2 H), 1.70−1.50 (m, 2 H), 1.40−1.25 (m, 5 H), 1.20 (t, J = 7.3 Hz, 3 H), 0.92 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 154.0 (s), 153.3 (s), 133.7 (d), 128.5 (d), 112.9 (t), 106.1 (d), 65.9 (t), 63.7 (t), 38.0 (t), 31.9 (d), 30.2 (t), 29.8 (t), 15.4 (q), 14.8 (q). MS m/z: 222 (M^+, 100), 111 (64). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.49; H, 10.36.

4-Ethyl-6-methyl-2,3,4,5,6,7-hexahydro-cyclopenta[*b*]-oxepin-8-one (75). This was obtained as a 3:1 diastereomeric mixture using the procedure described for **19** starting from **74** (84 mg, 0.38 mmol). Purification by flash chromatography (Et_2O−petroleum ether, 1:1, Et_3N 0.5%) gave **75** (48 mg, 65%, R_f = 0.38) as a white oil and **76** (7 mg, 9%, R_f = 0.54).

75. ^{1}H NMR (400 MHz, $CDCl_3$, δ) (major diastereoisomer): 4.32 (m, 1 H), 3.85 (m, 1 H), 2.75−2.60 (m, 2 H), 2.31 (m, 1 H), 2.22 (m, 1 H), 1.95 (dd, J = 16.3, 1.8 Hz, 1 H), 1.70−1.55 (m, 2 H), 1.39 (m, 1 H), 1.28−1.15 (m, 2 H), 1.01 (d, J = 6.95 Hz, 3 H), 0.90 (t, J = 6.5 Hz, 3 H). ^{13}C NMR (100.4 MHz, $CDCl_3$, δ) (major distereoisomer): 202.4 (s), 154.7 (s), 154.1 (s), 71.7 (t), 41.4 (t), 38.4 (t), 36.7 (d), 35.4 (d), 33.9 (t), 29.7 (t), 19.8 (q), 11.6 (q). MS m/z: 194 (M^+, 100), 109 (45).

76. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.97 (dqd, J = 16.1, 6.5, 1.8 Hz, 1 H), 6.72 (dd, J = 15.9, 1.8 Hz, 1 H), 6.25 (ddd, J = 10.2, 4.8, 1.8 Hz, 1 H), 4.25 (m, 1 H), 3.81 (m, 1 H), 2.14−2.03 (m, 2 H), 1.89 (d, J = 6.5 Hz, 1 H), 1.38−1.30 (m, 5 H), 0.90 (t, J = 6.5 Hz, 3 H). ^{13}C NMR (100.4 MHz, $CDCl_3$, δ): 187.6 (s), 157.3 (s), 144.2 (d), 128.5 (d), 119.1 (t), 71.5 (t), 37.5 (t), 37.1 (d), 31.6 (q), 29.0 (t), 18.6 (t), 11.3 (q). MS m/z: 194 (M^+, 18), 69 (100).

(*E*)-6-(1-Ethoxy-2-methyl-buta-1,3-dienyl)-3,4-dihydro-2*H*-pyran (77). This compound was prepared as described for **18** starting from **16** (166 mg, 0.5 mmol) and dienylboronate **12c** (112 mg, 0.5 mmol). After purification by flash chromatography (Et_2O−petroleum ether 1: 9, 0.5% Et_3N, R_f = 0.86) pure **77** (62 mg, 64% yield) was obtained as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.80 (dd, J = 15.7, 10.8 Hz, 1 H), 5.03 (dd, J = 15.7, 1.8 Hz, 1 H), 4.95−4.85 (m, 2 H), 4.05 (t, J = 6.1 Hz, 2 H), 3.78 (q, J = 7.3 Hz, 2 H), 2.14 (m, 2 H), 1.87−1.84 (m, 2 H), 1.81 (s, 3 H), 1.23 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (100.4 MHz, $CDCl_3$, δ): 150.1 (s), 146.3 (s), 136.2 (s), 119.1 (d), 110.6 (t), 106.3 (d), 66.1 (t), 64.6 (t), 22.3 (t), 21.7 (t), 15.5 (q), 10.7 (q). MS m/z: 194 (M^+, 100), 107 (100). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.33; H, 9.09.

(5*S,6*R**)-5,6-Dimethyl-3,4,5,6-tetrahydro-2*H*-cyclopenta[*b*]pyran-7-one (78).** This compound was obtained as described for **19** starting from **77** (63 mg, 0.32 mmol). Purification by flash chromatography (Et_2O−petroleum ether 1:1, 0.5% Et_3N) gave pure **78** (25 mg, 45%, R_f = 0.38) as a white oil and **79** (13 mg, 21%, R_f = 0.42).

78. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.15 (m, 1 H), 4.03 (m, 1 H), 2.82 (pent, J = 6.2 Hz, 1 H), 2.50 (pent, J = 6.2 Hz, 1 H), 2.38 (dt, J = 18.0, 5.6 Hz, 1 H), 2.22 (dt, J = 18.0, 5.9 Hz, 1 H), 2.00−1.94 (m, 2 H), 1.08 (d, J = 7.0 Hz, 3 H), 1.04 (d, J = 7.0 Hz, 3 H). ^{13}C NMR (100.4 MHz, $CDCl_3$, δ): 203.3 (s), 166.8 (s), 149.8 (s), 66.9 (t), 42.2 (d), 36.1 (t), 22.0 (d), 21.7 (t), 14.9 (q), 11.3 (q). MS m/z: 166 (M^+, 55), 151 (100). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.51; H, 8.45.

79. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.12−4.06 (m, 2 H), 2.38 (dt, J = 18.0, 5.9 Hz, 1 H), 2.26 (qd, J = 7.0, 1.8 Hz, 1 H), 2.21 (dt, J = 18.0, 5.9 Hz, 1 H), 1.98−1.94 (m, 2 H), 1.94 (qd, J = 7.0, 1.8 Hz, 1 H), 1.19 (d, J = 7.0 Hz, 3 H), 1.18 (d, J = 7.0 Hz, 3 H) ^{13}C NMR (100.4 MHz, $CDCl_3$, δ): 202.2 (s), 165.8 (s), 147.8 (s), 67.6 (t), 41.8 (d), 37.7 (t), 23.2 (d), 21.4 (t), 15.5 (q), 12.8 (q). MS m/z: 166 (M^+, 57), 151(100). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.43; H, 8.46.

6-(1-Ethoxyhexa-1,3-dienyl)-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Benzyl Ester (82). This compound was prepared as described for **18** starting from 6-trifluoromethanesulfonyloxy-3,4-dihydro-*2H*-pyridine-1-carboxylic acid benzyl ester[9a] (182 mg, 0.5 mmol) and **12d** (112 mg, 0.5 mmol). After purification by flash chromatography (Et_2O−petroleum ether 1:9, 0.5% Et_3N, R_f = 0.86) pure **82** (133 mg, 78%) was obtained as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.25 (s, 5 H), 6.11 (m, 1 H), 5.45 (d, J = 10.8 Hz, 1 H), 5.31 (t, J = 4.5

Hz, 1 H), 5.21 (m, 1 H), 5.15 (s, 2 H), 3.65 (q, $J = 6.9$ Hz, 2 H), 3.55 (m, 2 H), 2.32−2.16 (m, 2 H), 2.12 (pent, $J = 6.9$ Hz, 2 H), 1.96−1.70 (m, 2 H), 1.35 (t, $J = 6.9$ Hz, 3 H), 0.96 (t, $J = 6.9$ Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 155.9 (s), 152.2 (s), 140.1 (s), 133.9 (s), 131.5 (d), 128.9 (d), 128.4 (d), 124.8 (d, 2 C), 118.8 (d, 2 C), 108.0 (t), 104.3 (d), 99.8 (d), 68.0 (t), 63.8 (t), 23.8 (t), 23.2 (t), 22.9 (t), 22. 6 (q), 15.2 (q). MS *m*/*z*: 341 (M^+, 1), 91 (100). Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.65; H, 8.16; N, 3.99.

7-Oxo-5-propyl-2,3,4,5,6,7-hexahydro[1]pyrindine-1-carboxylic Acid Benzyl Ester (84). This compound was prepared as described for **19** starting from **82** (133 mg, 0.39 mmol). Purification by flash chromatography (Et_2O−petroleum ether 1:1, 0.5% Et_3N) gave pure **84** (56 mg, 45%, $R_f = 0.38$) as a white oil and **86** (11 mg, 9%, $R_f = 0.56$).

84. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.20 (s, 5 H), 5.12 (s, 2 H), 3.63−3.58 (m, 2 H), 2.65 (dd, $J = 17.6$, 6.2 Hz, 1 H), 2.45 (m, 1 H), 2.35 (m, 1 H), 2.11 (d, $J = 17.6$ Hz, 1 H), 2.00−1.89 (m, 2 H), 1.66 (m, 1 H), 1.45−1.18 (m, 4 H), 0.92 (t, $J = 6.8$ Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 202.1 (s), 161.4 (s), 156.2 (s), 139.1 (s), 136.9 (s), 129.2 (d, 2 C), 129.1 (d, 2 C), 128.8 (d), 68.7 (t), 44.9 (t), 41.1 (t), 39.3 (t), 30.8 (d), 30.2 (t), 29.2 (t), 14.9 (q). MS *m*/*z*: 313 (M^+, 9), 226 (100). Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 73.10; H, 7.38; N, 4.45.

86. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.25 (s, 5 H), 5.85 (t, $J = 5.3$ Hz, 1 H), 5.45 (m, 2 H), 5.25 (s, 2 H), 3.65 (t, $J = 6.5$ Hz, 2 H), 2.25 (m, 2 H), 2.01 (m, 2 H), 1.85 (m, 4 H), 0.90 (t, $J = 6.5$ Hz, 3 H). ^{13}C NMR (50.33 MHz, $CDCl_3$, δ): 180.2 (s), 152.2 (s), 149.2 (d), 144.7 (s), 138.1 (s), 131.9 (d), 130.5 (d), 126.9 (d, 2 C), 126.3 (d, 2 C), 120.9 (d), 73.5 (t), 48.5 (t), 35.1 (t), 32.1 (t), 27.1 (t), 25.4 (t), 19.0 (q). MS *m*/*z*: 313 (M^+, 5), 91 (100).

X-ray Crystallographic Determination of Compound 47. The crystallographic parameters are as follows: $C_{17}H_{21}NO_3S$, $M = 319.41$, monoclinic, space group $P2_1/n$, $a = 7.528(2)$ Å, $b = 27.765(5)$ Å, $c = 8.662(2)$ Å, $\beta = 112.30(2)°$, $V = 1675.1(7)$ Å^3, $Z = 4$, $D_c = 1.267$, $\mu = 0.205$ mm^{-1}, $F(000) = 680$.

Analysis on a single transparent light-yellow crystal was carried out with an Enraf Nonius CAD4 X-ray diffractometer at room temperature. Graphite-monochromated Mo Kα radiation was used for cell parameter determination and data collection. The intensities of two standard reflections were monitored during data collection to check the stability of the crystal: no loss of intensity was recognized. The integrated intensities, measured using a nonprofiled $\omega/2\theta$ scan mode, were corrected for Lorentz and polarization effects.[30] The reflections collected were 3870 with a range of $2.65 < \theta < 26.97$; 3646 reflections were independent, and the parameters were 232. The completeness to $\theta = 26.97$ was 99.8%. The final R index was 0.0503 for reflections having $I > 2\sigma I$ and 0.1036 for all data. The non-hydrogen atoms were refined anisotropically; aromatic and methyl hydrogens were assigned in calculated positions whereas the hydrogens on C_3, C_4, C_5, C_7, and C_8 were found in the Fourier difference synthesis, and all of them were refined as isotropic. Data were elaborated using "WinGX-Routine XCAD4",[31] and the structure was solved by direct methods of SIR97[32] and refined using the full-matrix least squares on F^2 provided by SHELXL97.[33] Crystallographic data were deposited at Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K. and are available from there under the deposition number CCDC215686.

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Supporting Information Available: X-ray crystallographic information file and ORTEP plot for **47**; ^{1}H NMR spectra of compounds **11**, **16**, **21**, **22**, **24**, **27**, **33**, **42**, **43**, **46**, **47**, **57**−**60**, **66**, **67**, **73**, **78**, and **79**. This material is available free of charge via the Internet at http://pubs.acs.org.

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