Highly Enantioselective Intermolecular Cu(I)-Catalyzed Cyclopropanation of Cyclic Enol Ethers. Asymmetric Total Synthesis of (+)-Quebrachamine

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A set of cyclic enol ethers derived from 2,3-dihydrofuran **35** and 3,4-dihydropyran **8** with a varying substitution pattern at the olefinic system were synthesized. Evans's ligand **5** with Cu(I)OTf was found to be an effective catalyst in the cyclopropanation reaction between cyclic enol ethers **14**, **19**, **28**−**31**, and **33** and ethyl diazoacetate **6** to give diastereoselectivities up to *exo*/*endo* = 95:5 and enantioselectivities higher than 95% in nearly all cases. Because of the selective building of a quarternary carbon center and good yields in the formation of bicyclic structures **34c**−**h**, the reaction was used as a key step in the asymmetric synthesis of (+)-quebrachamine **7**, an indole alkaloid of the Aspidosperma family. After acid-induced ring opening of bicyclic compound **34f** to lactone **40** followed by $LiAlH_4$ reduction to the masked aldehyde **41**, a reaction with tryptamine gave intermediate **42**. This alcohol was efficiently converted into the indole alkaloid (+)-quebrachamine **7** in an overall yield of 37% starting from the chiral synthon **34f**. Moreover it revealed the absolute configuration of the quarternary center of the cyclopropanation product **34f** to be *S*.

Introduction

The enantioselective [2 + 1] cycloaddition of carbenes to olefins is a synthetically useful reaction since two new carbon−carbon bonds and potentially up to three chiral centers are formed in one step and the resulting three-membered ring systems occur in many natural products and biologically active compounds.[1] Moreover, ring opening reactions with the preservation of the stereochemistry further increases the scope of cyclopropanes as useful intermediates in organic synthesis.[2] The asymmetric cyclopropanation catalyzed by a chiral transition metal complex is a very expedient route to enantiomerically pure cyclopropanes.[3] The first example was reported by Nozaki et al. in 1966 using a copper(II) complex of the chiral Schiff base **1** as the catalyst in the reaction between a diazo ester and an alkene to form cyclopropanes.[4] Then Aratani et al. optimized the ligand design of the chiral copper(II) complexes and achieved the first high enantioselectivities in the intermolecular cyclopropanation reactions using Schiff base **2**.[5] Further studies[3,6] have led to a variety of interesting regio- and stereoselective transition metal catalyzed cyclopropanation reactions. The most important progress was made with the introduction of Cu(I) chelated by C_2-symmetric semicorrins[7] **3** and bisoxazolines[8] **4** and **5** as chiral catalysts in the asymmetric cyclopropanation of alkenes with diazo esters (Figure 1).

Donor−acceptor substituted cyclopropanes have proved to be excellent building blocks for the synthesis of many functionalized molecular structures.[9] Reissig et al. developed a highly enantioselective cyclopropanation of silyl enol ethers[10] which led to interesting 1,4-difunctionalized carbonyl compounds after ring opening of the three-membered ring.[11] Evans's bisoxazoline ligand **5**/Cu(I)-OTf was found to be the most effective catalyst for the addition of carbenes to silyl enol ethers. The first and only study—to the best of our knowledge—of the asymmetric cyclopropanation of enol ethers was also made by Reissig et al.[12] The reaction between Z1-propenyl ethers and methyl diazoacetate led to good *trans*-selectivities, moderate yields, but low enantioselectivities. Moreover,

(1) (a) Lin, H. W.; Walsh, C. T. In *The Chemistry of the Cyclopropyl Group*; Patai, S., Rappaport, Z., Eds.; Wiley: New York, 1987. (b) Saluen, J. *Chem. Rev.* **1989**, *89*, 1247.

(2) Wong, H. N. C.; Hou, M.-Y.; Tse, C.-W.; Yip Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.

(3) (a) Singh, K. V.; Datta Goupta, A.; Sekar, G. *Synthesis* **1997**, 137. (b) Doyle, M. P. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993, 63. (c) Reissig, H. U. In *Stereoselective Synthesis, Houben-Weyl*; Helmchen, G., Hoffmann R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart 1996; E21, Vol. 5, p 3179. (d) Doyle, M. P. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; 1995; Vol. 12, p 387.

(4) Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1966**, 5239.

(5) (a) Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1975**, 1707. (b) Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1977**, 2599.

(6) Some recent papers: (a) Ashutosh, V. B.; Koroleva, E. B.; Andersson, P. G. *J. Org. Chem.* **1997**, *62*, 2518. (b) Ichiyanagi, T.; Shimizu, M.; Fujisawa, T. *Tetrahedron* **1997**, *53*, 9599. (c) Fraile, J. M.; Garcia, J. I.; Mayoral, J. A.; Tarnai, T. *Tetrahedron: Asymmetry* **1997**, *8*, 2089. (d) Bolm, C.; Pupowicz, D. *Tetrahedron Lett.* **1997**, *38*, 7349. (e) Aggarwal, K. V.; Smith, H. W.; Jones, R.; Fieldhouse, R. *Chem. Commun.* **1997**, 1785. (f) Frauenkron, M.; Berkessel, A. *Tetrahedron Lett.* **1997**, *38*, 7175. (g) Haddad, N.; Galili, N. *Tetrahedron: Asymmetry* **1997**, *8*, 3367. (h) Pyne, S. G.; Dong, Z.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **1997**, *62*, 2337. (i) Denmark, S. E.; O'Connor, S. P. *J. Org. Chem.* **1997**, *62*, 3390.

(7) (a) Frischi, H.; Leuteneggar, U.; Pfaltz A. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1005. (b) Frischi, H.; Leuteneggar, U.; Pfaltz A. *Helv. Chim. Acta* **1988**, *71*, 1553.

(8) (a) Mueller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232. (b) Lowenthal, R. E.; Aibko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005. (c) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, 7373. (d) Evans, D. A.; Woerpel, K. A.; Hinman, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (e) Evans, D. A.; Woerpel, K. A.; Scott, M. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 430.

(9) Reissig, H. U. *Top. Curr. Chem.* **1988**, *144*, 75.

(10) (a) Schumacher, R.; Dammast, F.; Reissig, H. U. *Chem. Eur. J.* **1997**, *3*, 614. (b) Schumacher, R.; Reissig, H. U. *Liebigs Ann./Receuil* **1997**, 521.

(11) Dammast, F.; Reissig H. U. *Chem. Ber.* **1993**, *126*, 2249.

(12) Schumacher, R.; Reissig, H. U. *Synlett* **1996**, 1121.

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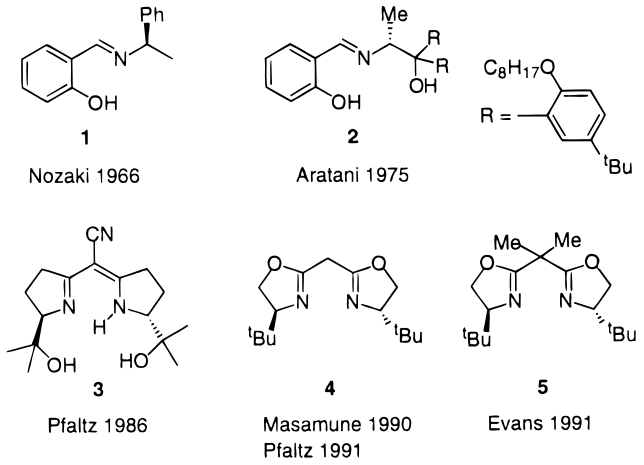


Figure 1. Chiral ligands for Cu(I)-catalyzed asymmetric cyclopropanations with diazomethane esters.

the absolute configuration of the cyclic products was not determined.

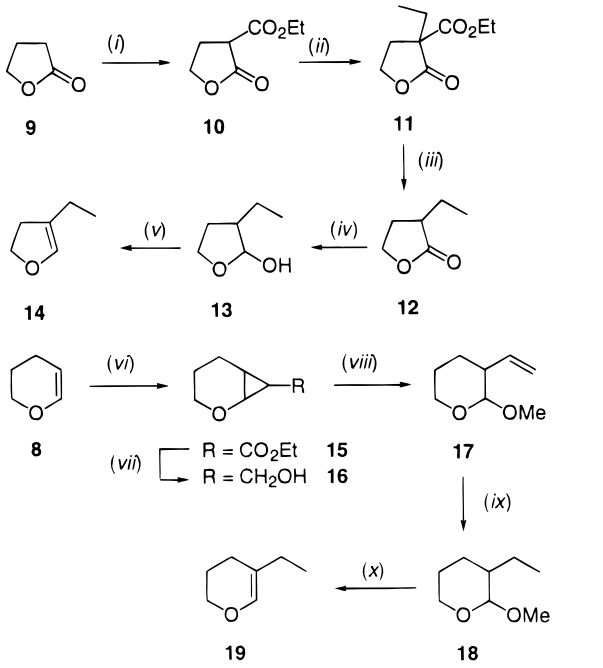
In this paper we present the first study of the synthesis and highly stereo- and enantioselective cyclopropanation of cyclic enol ethers using ethyl diazoacetate **6** and Evans's bisoxazoline ligand **5**/Cu(I)OTf as the catalyst. Furthermore, the absolute configuration of the bicyclic products was determined via the total synthesis of the natural product (+)-quebrachamine **7**.

Results and Discussion

Synthesis of Cyclic Enol Ethers as Cyclopropanation Precursors. Enol ethers are useful intermediates in organic synthesis because they show interesting behavior in cycloadditions and reactions with electrophiles due to the unusual polarity of the olefinic system.[13] Cyclic enol ethers are by far the most stable compounds of this class, and 3,4-dihydropyran **8** is even often used as a protecting group for primary and secondary alcohols in organic synthesis.[14] However, only a few short studies about the synthesis of cyclic enol ethers with different substitution patterns have been reported.[15] First we chose two synthetic routes developed by Wenkert et al.[16] and Zenk and Wiley[17] for the formation of an ethyl-substituted pyran and furan ring system (Scheme 1) to compare them in the cyclopropanation with diazo esters.

Enol ether 4-ethyl-2,3-dihydrofuran **14** was synthesized via the alkylated butyrolactone **12** followed by reduction with DIBALH and elimination via the tosylate. The 5-ethyl-3,4-dihydropyran **19** was prepared by the route developed by Wenkert et al. where the alkyl group is introduced via the cyclopropanation of 3,4-dihydropyran **8** with ethyl diazoacetate. Subsequent reduction with lithium aluminum hydride, acid-induced ring opening, and hydrogenation of the resulting olefin **17** gave **18** in which the methoxy group was eliminated to afford the final enol **19**. In both cases, for the synthesis of enol ethers **14** and **19**, the overall yield could be improved after slight changes of the literature procedures.

Scheme 1[a]



[a] Reagents: (i) Na, diethyl carbonate, H_2SO_4 concd, 46%; (ii) acetone, NaI, EtI, K_2CO_3, reflux, 97%; (iii) ethanol, 2 M NaOH, reflux, 39%; (iv) THF, DIBAL, 90%; (v) quinoline, *p*-TsOH, 190 °C, 32%; (vi) $CuSO_4$, N_2CHCO_2Et, reflux, 90%; (vii) diethyl ether, $LiAlH_4$, 99%; (viii) 0.5 M H_2SO_4 in methanol, 60 °C, 60%; (ix) ethyl acetate, 2.4 mol % PtO_2, 120 psi H_2, 96%; (x) quinoline, *p*-TsOH, 190 °C, 92%.

The main target was to find a short and efficient route which would allow the preparation of a series of cyclic enol ethers with different substituents at the olefinic system. Following a literature procedure,[18] 4-benzyl-2,3-dihydrofuran **29** was prepared via a three-step procedure (Scheme 2). Deprotonation of butyrolactone **9** with LDA and addition of an electrophile resulted in the alkylated lactone **21**. Subsequent reduction with DIBALH gave alcohol **25** which was subjected to mesylation and elimination to give the desired enol ether **29**. By variation of the electrophile (MeI, *n*-PrI) and the ring size of the starting lactone **9a,b** a series of alkylated lactones **20**−**23** was prepared. The reduction to alcohols **24**−**27** always resulted in high yields. The final elimination was either done via the tosylate at high temperatures as in the case of **28** or via the mesylate under milder conditions to give enol ethers **29**−**31**. This reaction sequence proved to be a short and efficient way to 4-substituted dihydrofuran and 5-substituted dihydropyran structures.

Pyrans having a substituent at the 6-position of the ring was prepared via lithiation of the corresponding five- or six-membered cyclic enol ether. Following a literature procedure,[19] 3,4-dihydropyran **8** was treated with *n*-BuLi

(13) (a) March, J. In *Advanced Organic Chemistry*, 4th ed.; Wiley: New York 1992; pp 856 and 871. (b) Carey, F. A.; Sundberg, R. J. In *Advanced Organic Chemistry*, 3rd ed.; Plenum Press: New York 1989; Part B., p 693.

(14) Green, T. W. In *Protective Groups In Organic Synthesis*; Wiley: New York, 1981; p 22.

(15) (a) Hall, S. S.; Weber, G. F.; Duggar, A. J. *J. Org. Chem.* **1978**, *43*, 667. (b) Longley, R. I.; Emerson, W. S. *J. Am. Chem. Soc.* **1950**, *72*, 9. (c) Parham, W. E.; Holmquist, H. E. *J. Am. Chem. Soc.* **1951**, *73*, 3. (d) Weber, G. F.; Hall, S. S. *J. Org. Chem.* **1979**, *44*, 364. (e) Botthegi, C.; Consiglio, G.; Ceccarelli, G.; Stefani, A. *J. Org. Chem.* **1972**, *37*, 1835. (f) Baird, M. S.; Baxter, A. G. W.; Hoorfar, A.; Jefferies, I. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2575.

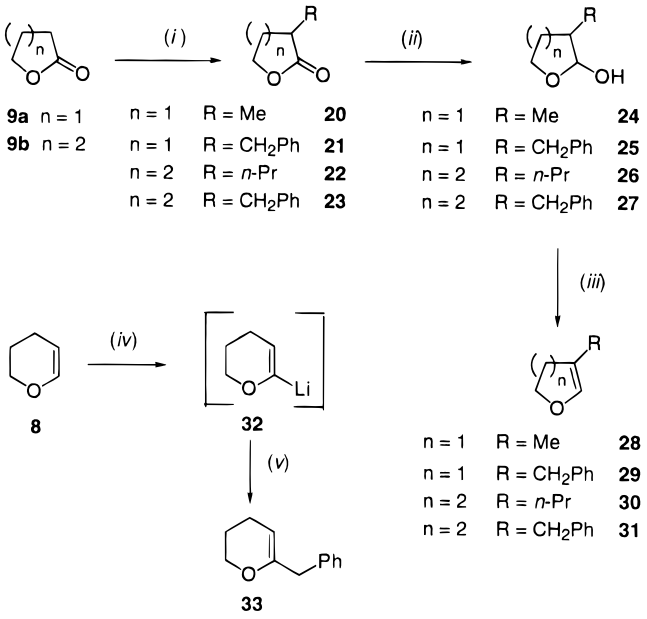
(16) Wenkert, E.; Buckwalter, B. L.; Sathe, S. S. *Synth. Commun.* **1973**, 261.

(17) Zenk, P. C.; Wiley: R. A. *Chem. Commun.* **1984**, 695.

(18) Takacs, J. M.; Newsome, P. W.; Kuehn, C.; Takusagawa, F. *Tetrahedron* **1990**, *46*, 5507.

(19) Oakes, F. T.; Sebastian, J. F. *J. Org. Chem.* **1980**, *45*, 4959.

Scheme 2[a]



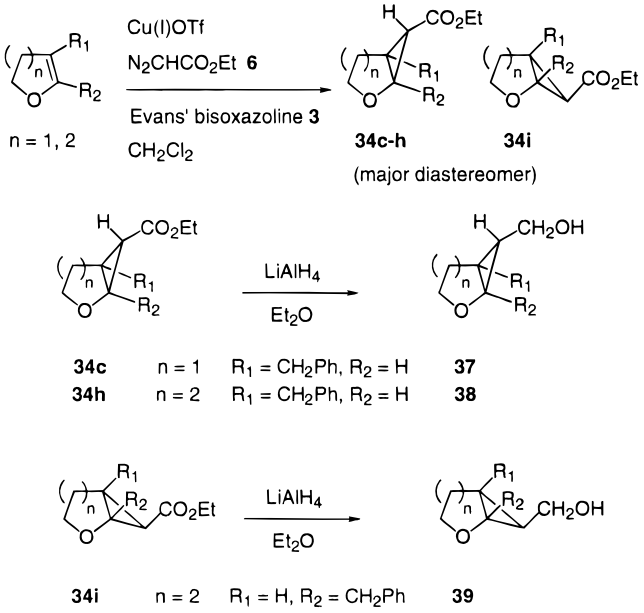
[a] Reagents: (i) THF, LDA, **20**: MeI, 67%, **21**: HMPA, $PhCH_2Br$, 69%, **22**: HMPA, *n*-PrI, 23%, **23**: $PhCH_2Br$, 82%; (ii) THF, DIBAL, 90−98%; (iii) **28**: quinoline, *p*-TsOH, 190 °C, 35%, **29**−**31**: benzene, TEA, DMAP, MsCl, 24−63%; (iv) TMEDA, n-BuLi, hexane; (v) diethyl ether, $PhCH_2Br$, 72%.

to furnish the white lithium salt **32** after removal of the solvent. A subsequent reaction with MeI has been described in the literature.[19] All our attempts to purify the product failed. The only enol ether with this substitution pattern which was successfully purified was 6-benzyl-3,4-dihydropyran **33** formed in the reaction between benzyl bromide and lithium salt **32** (Scheme 2).

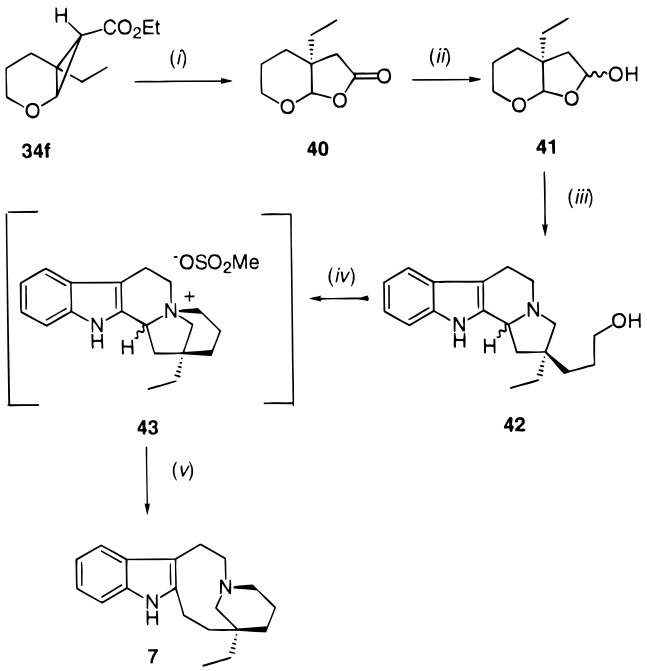
Asymmetric Cyclopropanation of Cyclic Enol Ethers. From the large number of C_2-symmetric ligands for enantioselective intermolecular cyclopropanation (Figure 1) we selected Evans's bisoxazoline **3** which had been proved to be the most effective ligand for Cu(I)OTf in the reaction of diazo esters with many different olefins.[3,8] Following a literature procedure developed by Pfaltz et al.,[20] 2 mol % of the active catalyst and a slight excess of the diazo compound were used in the cyclopropanation of cyclic enol ethers in CH_2Cl_2 (Scheme 3, Table 1).

Enol ethers 3,4-dihydropyran **8** and 2,3-dihydrofuran **35** gave the desired cyclopropanes in good yields (77% of the isolated major diastereomer) and high *exo* selectivity (Table 1, entries 1 and 2), but unfortunately without any asymmetric induction. However, when the alkyl-substituted enol ethers were used as substrates, the cyclopropanation reaction with ethyl diazoacetate **6** proceeded with high enantioselectivity in nearly all cases. The only asymmetric cyclopropanations of enol ethers reported so far by Reissig et al.[12] were a reaction between Z1-propenyl ethers and methyl diazoacetate in the presence of Evans's catalyst. Next to moderate yields (48 and 54%) and a good stereoselectivity (up to 3:97 *trans*-selectivity) the enantioselectivity was rather poor (32 and 40% of the *trans*-enantiomer). Cyclopropanation of both 4-substituted dihydrofurans and 5-substituted dihydropyrans resulted in the formation of **34c**−**h** as the major diastereomers in ee's higher than 95% (Table 1, entries 3−8). These values are surprisingly high for the enantioselective formation of a quarternary carbon center compared to cyclopropanation reactions of corresponding silyl enol ethers with Evans's ligand **3**/Cu(I)OTf.[10] No dependence between the enantioselectivity and the size of the substituents could be observed. On the contrary, 1,1-disubstituted silyl enol ethers which gave good results in the asymmetric cyclopropanation with Evans's catalyst[10] gave rise to lower selectivities (74%) in the reaction of 6-benzyl-3,4-dihydropyran **33** with ethyl diazoacetate **6** (Table 1, entry 9). The determination of the enantio-

Scheme 3



Scheme 4[a]



[a] Reagents: (i) 10% H_2SO_4, dioxane, reflux 15 h; (ii) diethyl ether, DIBAL, −78 °C; (iiia) tryptamine hydrochloride, 10% aqueous acetic acid; (iiib) 10% aqueous acetic acid, $NaBH_3CN$; (iv) $CHCl_3$, TEA, MsCl, 40 h, rt; (v) *N*-methylmorpholine, $LiAlH_4$, reflux, 13 h (37% overall yield).

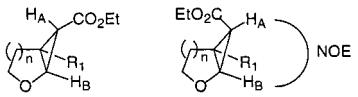
(20) Leutenegger, U.; Umbricht, G.; Fahrni, C.; Matt, P.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143.

Table 1. Results of the Asymmetric Cyclopropanation Reactions

entry	olefin	R_1	R_2	n	product yield (%)[a]	*endo*/*exo*[b]	ee (%)
1	**35**	H	H	1	**34a** (77)	12 : 88	rac
2	**8**	H	H	2	**34b** (77)	13 : 87	rac
3	**28**	Me	H	1	**34c** (60)	30 : 70	> 95[c]
4	**13**	Et	H	1	**34d** (57)	28 : 72	> 95[c]
5	**29**	CH_2Ph	H	1	**34e** (77)	21 : 79	96[d]
6	**19**	Et	H	2	**34f** (52)	9 : 91	> 95[c]
7	**30**	*n*-Pr	H	2	**34g** (54)	6 : 94	> 95[c]
8	**31**	CH_2Ph	H	2	**34h** (67)	5 : 95	96[d]
9	**33**	H	CH_2Ph	2	**34i** (45)	7 : 93	74[d]

[a]Isolated yield of the major diastereomer after flash chromatography. [b]Determined by GC analysis, NMR coupling constants, NOE- and NOESY-experiments. [c]Determined by using NMR spectroscopy after titration with chiral shift reagent Eu(hfc)$_3$. [d]Determined via HPLC analysis (HPLC: chiral OD-H column, hexane / *i*-PrOH 80:20, 0.4 ml/min) of alcohol derivatives **37**, **38** and **39** after $LiAlH_4$ reduction. [e]General procedure for the asymmetric cyclopropanation to **34** and reduction with $LiAlH_4$ to **37** - **39** see experimental.

Table 2. ^{1}H NMR Data To Prove the Stereochemical Outcome of the Reaction



major minor

entry	product	R	n	δ H_A (ppm)	δ H_B (ppm)	J_{AB} (Hz)
1	**34c**	Me	1	4.04	1.96	1.7
2	**34d**	Et	1	3.81	1.80	2.9
3	**34e**	CH_2Ph	1	4.31	2.12	1.7
4	**36**	CH_2Ph	1	4.09	1.68	7.7
5	**34f**	Et	2	3.80	1.78	2.9
6	**34g**	*n*-Pr	2	4.11	1.92	2.9
7	**34h**	CH_2Ph	2	4.17	1.98	3.0

meric excesses was carried out by titration with Eu(hfc)$_3$ (Table 1, entries 1−4, 6, 7) and HPLC analysis of the alcohol derivatives **37**−**39** (Table 1, entries 5, 8, 9).

The high *exo* selectivity of the [2 + 1] addition was expected as similar observations[3,8,21] have been reported for various metal-catalyzed reactions of diazoesters. The *exo* orientation of the ester group of **34c**−**h** was determined on the basis of the proton−proton coupling of the cyclopropane protons (Table 2). All major isomers showed a J_{AB} ranging from 1.7 to 3.0 Hz which is consistent with a *trans*-coupling for this type of compound.[22]

In the cyclopropanation of 4-benzyl-2,3-dihydrofuran **29** the minor diastereomer **36** was isolated and determined to be of an enantiomeric excess greater than 95%. The *endo* orientation of the ester moiety of the minor

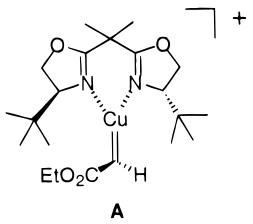


Figure 2. Reactive complex **A** in the asymmetric cyclopropanation with Evans's ligand **3**, Cu(I)OTf, and ethyl diazoacetate **6**.

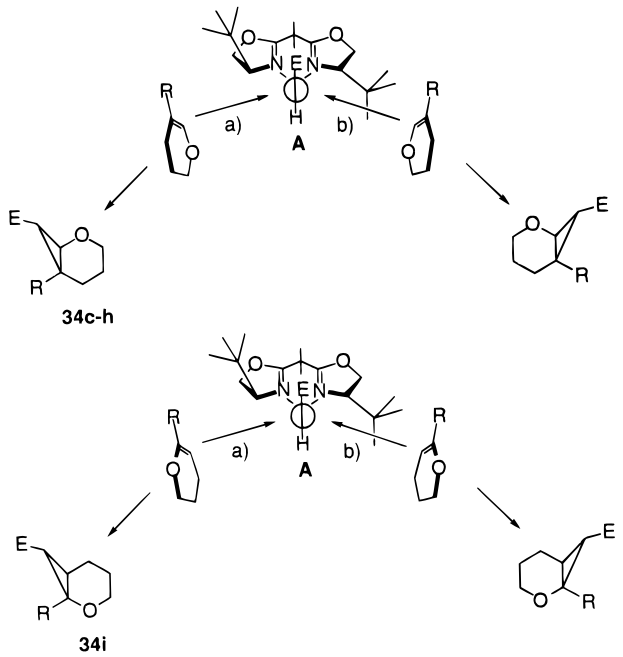


Figure 3. Application of Pfaltz model on the asymmetric cyclopropanation between alkyl-substituted pyrans and reactive complex **A**.

isomer **36** was assigned not only based on the large J_{AB} (7.7 Hz) but also by NOE difference spectroscopy. A strong enhancement of H_A was observed upon irridiation of H_B and vice versa. Such an enhancement could not be observed for the major isomers. In general the pyran systems showed a higher *exo* selectivity (up to 95:5) than the five-membered analogues.

Mechanistic Aspects. The cyclic enol ethers showed a high reactivity in the copper-catalyzed cyclopropanation with ethyl diazoacetate **6**, undoubtedly because the copper carbene complex **A** (Figure 2) is highly electrophilic and readily reacts with the electron rich double bond.

Various models have been suggested for the approach of reactive complex **A** to alkenes.[23] We found our results to be in accordance with the model proposed by Pfaltz for asymmetric cyclopropanations.[23c] Figure 3 shows the application of this model to a reaction between an alkyl-substituted pyran and a Cu(I)-complex formed from ethyl diazoacetate **6** and Evans's bisoxazoline **3**.

Pathway a is expected to be favored over b since the transition state of pathway b shows a strong repulsive steric interaction between the approaching olefin and the ^{t}Bu group of the ligand. This model also indicates that

(21) (a) Demonceau, A.; Noels, A. F.; Hubert, A. J. *Tetrahedron* **1990**, *46*, 3889. (b) Doyle, M. P.; Bagheri, T. J.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K. L. *J. Am. Chem. Soc.* **1990**, *112*, 1906. (c) Maas, G.; Werle, T.; Alt, M.; Mayer, D. *Tetrahedron* **1993**, *49*, 881.

(22) Guenther, H. In *NMR−Spektroskopie*; Thieme: Stuttgart, 1992; 3.Aufl., p 109.

(23) (a) Aratani, T. *Pure Appl. Chem.* **1985**, *57*, 1839. (b) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. (c) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta* **1988**, *71*, 1533.

the high enantioselectivity depends on the structure of the olefin. In contrast to the alkenes **8** and **35** which gave no enantioselectivity (Table 1, entries 1 and 2), the introduction of a third substituent R makes it possible to control the outcome of the reaction since it is obviously favorable that the substituent R will be pointing away from the ligand framework which leads to high enantioselectivities. On the basis of this model we assume that enol ethers having a substituent at the same carbon bearing the ether function will result in the opposite face-selection resulting in **34i**.

The *endo*/*exo* selectivity is expected to be dominated by the interactions between the substituents at the enol double bond and the carbenoid moiety. The reaction is highly *exo* selective since a furan or pyran ring is sterically more demanding than a flexible alkyl substituent. For that reason the heterocycle is pointing away from the ester function leading to *exo* cyclopropanes. Due to the larger ring size, pyrans show higher *exo* selectivity than furan structures.

Synthesis of (+)-Quebrachamine. Determination of the Absolute Configuration of the Asymmetric Cyclopropanation Products. To determine the absolute configuration of the bicyclic products **34**, we synthesized an Aspidosperma type indole alkaloid,[24] exploiting a route developed by Wenkert et al.[25] Many attempts have been made to develop an efficient synthesis of the Aspidosperma alkaloid quebrachamine **7**[26] since this class of alkaloids possess a variety of important physiological activities.[27] The Pictet−Spengler or the Bischler−Napieralski condensation of tryptamine developed by Kutney et al.[26a] is the most frequently used strategy and also the basis of the enantioselective synthesis of (+)-quebrachamine **7** by Fuji et al.[28a] The second reported enantioselective route to either (+)- or (−)- **7** is based on a reaction between tryptamine and a chiral template derived from L-glutamic acid.[28b,c]

The chiral center in quebrachamine **7** is a quarternary carbon with an ethyl group. Wenkert et al. developed a way to Aspidosperma alkaloids via γ-diketo compounds derived from oxycyclopropanes.[25] The enantiomerically pure cyclopropane **34f** seemed to us a good chiral synthon for the asymmetric total synthesis of quebrachamine **7**.

The acid-induced ring cleavage of **34f** gave lactone **40** in 77% yield. Reduction of lactone **40** with DIBALH was followed by acid-catalyzed condensation with tryptamine and subsequent reduction with sodium cyanoborohydride which led to the diastereomeric mixture of alcohols **42**. Kutney et al.[26a] developed a short two-step synthesis of (+)/(−)-quebrachamine **7** from alcohol **42** via the quarternary ammonium salt **43** formed spontaneously from the mesylate with methanesulfonyl chloride and triethylamine followed by a reductive cleavage utilizing $LiAlH_4$ in refluxing *N*-methylmorpholine. We found that the yield of this two-step route could be improved from 50 to 67% by avoiding a purification of the intermediate **43**. The final reductive cleavage to a nine-membered heterocyclic ring structure resulted in an overall yield of 37% of the desired natural product **7** with a single quarternary center formed in the previous cyclopropanation step. The positive optical rotation ($[\alpha]^{22}_D = +111$) manifested the product to be at least 94% enantiomerically pure (+)-quebrachamine **7** based on the literature value and revealed the absolute stereochemistry of the quarternary center of the cyclopropanation product **34f** to be *S* (Figure 4) which is in accordance with the prediction made from the model in Figure 3.

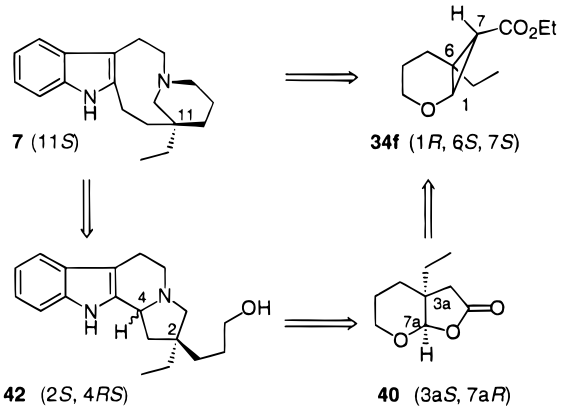


Figure 4. Determination of the absolute configuration of bicyclic cyclopropanation products **34c**−**h** via alkaloid quebrachamine.

It should also be noted that this strategy gives access to a number of Aspidosperma and Vincamine alkaloids in an optical active form since the quarternary ammonium salt **43** has previously been transformed into these indole alkaloids.[29]

Conclusions

Catalytic asymmetric cyclopropanation of dihydrofuran and dihydropyran structures using Cu(I)OTf/Evans's bisoxazoline ligand **3** as catalyst and ethyl diazoacetate **6** yielded bicyclic compounds **34c**−**i** with stereoselectivities up to 95:5 *exo* and ee's higher than 95% in nearly all cases. The excellent control of the absolute configuration at the key quarternary carbon at C(6) in **34f** allowed the asymmetric total synthesis of (+)-quebrachamine **7** in a five-step synthesis with an overall yield of 37%.

Experimental Section

For general experimental information, see ref 6a. Methylene chloride was dried over calcium hydride and freshly distilled under nitrogen. THF and diethyl ether were distilled

(24) Some recent papers concerning the total synthesis of Aspidosperma and vincamine alkaloids: (a) Schultz, A. G.; Liping, P. *J. Org. Chem.* **1997**, *62*, 6855. (b) Desmaele, D.; Mekonar, K.; D'Angelo, J. *J. Org. Chem.* **1997**, *62*, 3890. (c) Schultz, A. G.; Malachowski, W. P.; You, P. *J. Org. Chem.* **1997**, *62*, 1223.

(25) Wenkert, E.; Halls, T. D.; Kwart, L. D.; Magnusson, G.; Showalter, H. D. H. *Tetrahedron* **1981**, *37*, 4017.

(26) Racemic syntheses of quebrachamine **7**: (a) Kutney, J. P.; Abdurahman, N.; Le Quesne, P.; Piers, E.; Vlattas, I. *J. Am. Chem. Soc.* **1966**, *88*, 3656. (b) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T.; Takeda, E. *Tetrahedron* **1983**, *39*, 3657. (c) Ziegler, F. E.; Kloek, J. A.; Zoretic, P. A. *J. Am. Chem. Soc.* **1969**, *91*, 2342. (d) Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1976**, *98*, 3022. (e) Giri, V. S.; Ali, E.; Pakrashi, S. C. *J. Heterocycl. Chem.* **1980**, *17*, 1133.

(27) (a) Cordell, G. A. In *The Alkaloids*; Manske, R. H. F., Rodrigo, R. G. A., Eds.; Academic Press: New York, 1979; Vol. 17; p 199. (b) Neuss, N. In *Indole and Biogenetically Related Alkaloids*; Philipson, J. D., Zenk, M. H., Eds.; Academic Press: London, 1980. (c) Lohnasmaa, M.; Tolvanen, A. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York 1992; Vol. 42, p 1.

(28) Asymmetric syntheses of quebrachamine **7**: (a) Manabu, N.; Nagasawa, H.; Fuji, K. *J. Am. Chem. Soc.* **1987**, *109*, 7901. (b) Takano, S.; Chiba, K.; Yonaga, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1980**, 616. (c) Takano, S.; Chiba, K.; Yonaga, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1981**, 1153.

(29) (a) Kutney, J. P.; Chan, K. K.; Failli, A.; Fromson, J. M.; Gletsos, C.; Leutwiler, A.; Nelson, V. R.; de Souzu, J. P. *Helv. Chim. Acta* **1975**, *58*, 1648. (b) Mokry, J.; Kompis I. *Lloydia* **1964**, *27*, 428. (c) Danieli, B.; Lesma, G.; Palmisano, G. *J. Chem. Soc., Chem. Commun.* **1981**, 908. (d) Lewin, G.; Poisson, J. *Tetrahedron* **1984**, *25*, 3813.

over sodium/benzophenone under nitrogen. Ethyl diazoacetate **6**, $(CuOTf)_2 \cdot C_6H_6$, 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] **3**, and $Eu(hfc)_3$ were purchased from Aldrich Co. 3,4-Dihydropyran **8**, 2,3-dihydrofuran **35**, butyrolactone **9a**, and valerolactone **9b** as starting materials were purchased from Lancaster and freshly distilled just prior use.

Synthesis of Enol Ethers as Cyclopropanation Precursors. 2-Oxotetrahydrofuran-3-carboxylic Acid Ethyl Ester (10). To a vigorously stirred solution of sodium (11.5 g, 500 mmol) in diethyl carbonate (123 mL) at 100 °C was introduced dropwise γ-butyrolactone (43.5 g, 500 mmol) in diethyl carbonate (40 mL) over 3 h. The cooled reaction mixture was then poured into a mixture of ice-cold water (450 mL) and concentrated sulfuric acid (21 mL). The phases were separated, and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic phases were dried and concentrated in vacuo. Fractional distillation (bp 134−136 °C/8 mmHg) of the crude product afforded **10** (36.1 g, 46%) as a colorless oil. Physical and spectroscopic data of the product were in complete agreement with the literature data.[30]

3-Ethyl-2-oxotetrahydrofuran-3-carboxylic Acid Ethyl Ester (11). A solution of lactone **10** (15.8 g, 61 mmol) in acetone (250 mL) was treated with sodium iodide (30.0 g, 200 mmol), ethyl iodide (31.4 g, 200 mmol), and K_2CO_3 (34.5 g, 250 mmol) and then refluxed for 17 h. After cooling to room temperature, the reaction mixture was diluted with hexane (170 mL), filtered, and concentrated in vacuo. The residue was dissolved in pentane/ethyl acetate 1/1 and filtered again to give **11** (17.0 g, 97%) after concentration. Physical and spectroscopic data of the product were in complete agreement with the reported data.[17]

3-Ethyltetrahydrofuran-2-one (12). A solution of lactone **11** (24 g, 130 mmol) in ethanol (100 mL) was treated with 2 M aqueous NaOH (80 mL) and stirred at room temperature for 6 h. Most of the water and ethanol were removed in vacuo. The residue was treated with 10% aqueous sulfuric acid (33 mL) and refluxed for 12 h. After the mixture was cooled to room temperature, the product was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ and 2 M NaOH, dried over $MgSO_4$, and concentrated in vacuo to give **12** (5.7 g, 39%) as a colorless oil. All physical and spectroscopic data of the product were in complete agreement with the literature values.[17]

3-Ethyltetrahydrofuran-2-ol (13). A solution of lactone **12** (5.0 g, 44 mmol) in dry ether (50 mL) was treated with DIBALH (50 mL, 1 M solution in THF, 50 mmol) at − 20 °C and stirred for 1.5 h at this temperature. The resulting reaction mixture was slowly warmed to room temperature and then quenched with methanol (35 mL). After filtration, concentration of the solvent in vacuo afforded **13** (4.6 g, 90%) as a colorless oil. All the physical and spectroscopic data of the product were in complete agreement with the reported data.[17]

4-Ethyl-2,3-dihydrofuran (14). Lactone **13** (4.8 g, 41 mmol) was added dropwise to a solution of *p*-toluenesulfonic acid (0.02 g) in quinoline (2.5 mL) at 190 °C over 20 min. The product was simultaneously distilled out of the reaction mixture using a microdistillation assembly and collected in a round-bottom flask containing 2 M NaOH (5 mL). The receiver was cooled to −78 °C during the distillation. The distillate was extracted with ether (10 mL), the phases were separated, and the organic layer was dried over $MgSO_4$ and concentrated in vacuo to give **14** (1.3 g, 32%) as a colorless oil. All the physical and spectroscopic data of the product were in complete agreement with the reported data.[17]

7-Carbethoxy-2-oxabicyclo[4.1.0]heptane (15). To a refluxing solution of freshly distilled 3,4-dihydropyran **8** (37.8 g, 45 mmol) and $CuSO_4$ (0.6 g) was added slowly a mixture of ethyl diazoacetate **6** (8.5 g, 85 mmol) and 3,4-dihydropyran **8** (12.6 g, 150 mmol) over 2.5 h. The reaction mixture was refluxed for additional 2 h. Excess of 3,4-dihydropyran **8** was removed at atmospheric pressure and the crude product distilled (bp 88−92 °C/3 mmHg) to give **15** (11.4 g, 90%) as a colorless oil. All the physical and spectroscopic data of the product were in complete agreement with the reported data.[16]

7-(Hydroxymethyl)-2-oxabicyclo[4.1.0]heptane (16). To a suspension of $LiAlH_4$ (5.1 g, 130 mmol) in dry ether (45 mL) was added a solution of ester **15** (11.4 g, 67 mmol) in dry ether (25 mL) over a period of 3 h at 0 °C. After additional stirring at room temperature for 3 h, the reaction was quenched with H_2O (5 mL), 15% aqueous NaOH (5 mL), and H_2O (15 mL). The filtrate was carefully washed with ether, and the organic layer was concentrated. The crude product was purified by flash chromatography (pentane/ethyl acetate: 3/1) to give **16** (8.4 g, 99%) as a colorless oil. All the physical and spectroscopic data of the product were in complete agreement with the reported data.[16]

2-Methoxy-3-vinyl-3,4,5,6-tetrahydropyran (17). Alcohol **16** (19.6 g, 153 mmol) was treated with sulfuric acid (43 mL, 0.5 M solution in methanol) at 60 °C for 1.5 h. After addition of K_2CO_3 (5 g), the reaction mixture was stirred for 15 min, diluted with brine (50 mL), and extracted with CH_2Cl_2 (4 × 50 mL). The extracts were dried over $MgSO_4$ and concentrated, and the residue was distilled (bp 75−80 °C) to give **17** (13.3 g, 61%) as a colorless oil. All the physical and spectroscopic data of the product were in complete agreement with the reported data.[16]

2-Methoxy-3-ethyl-3,4,5,6-tetrahydropyran (18). Olefin **17** (17.3 g, 122 mmol) and PtO_2 (0.5 g, 2.4 mol %) in ethyl acetate (100 mL) were transferred into an autoclave, and the olefin was stirred under H_2 (120 psi) at room temperature for 12 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated to give **18** (16.8 g, 96%) as a colorless oil. Physical and spectroscopic data of the product were in complete agreement with the literature data.[16]

5-Ethyl-3,4-dihydropyran (19). Following the procedure described for **14**, pyran **18** (10.0 g, 69 mmol) gave **19** (4.4 g, 57%) as a colorless oil. Distillation of the quinoline residue gave another 2.7 g (35%) of pure **19** (bp 139−145 °C). All the physical and spectroscopic data of the product were in complete agreement with the reported data.[16]

3-Benzyldihydrofuran-2-one (21). To a solution of DIPA (5.6 g, 55 mmol) in dry THF (45 mL) at −78 °C was added dropwise *n*-BuLi (38 mL, 1.6 M solution in hexane, 61 mmol) over 20 min and stirred at this temperature for another 20 min. Then a solution of butyrolactone (4.3 g, 50 mmol) in dry THF (50 mL) was added over 30 min. After additional stirring at −78 °C for 20 min, benzyl bromide (10.3 g, 60 mmol) in HMPA (10 mL) was added dropwise over 15 min. The reaction mixture was stirred for 4 h while warming up to −30 °C. The reaction was allowed to come to room temperature, quenched by the addition of saturated aqueous NH_4Cl (25 mL), diluted with ether (50 mL), washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography (pentane/ethyl acetate: 85/15) to give **21** (6.1 g, 69%) as a colorless oil. All the physical and spectroscopic data of the product were in complete agreement with the literature data.[31]

3-Benzyltetrahydrofuran-2-ol (25). Following the procedure described for **13**, lactone **21** (6.5 g, 37 mmol) gave **25** (6.1 g, 93%) as a colorless oil after flash chromatography (pentane/ethyl acetate: 3/1). All the physical and spectroscopic data of the product were in complete agreement with the reported data.[32]

4-Benzyl-2,3-dihydrofuran (29). To a solution of lactol **25** (4.0 g, 23 mmol) in benzene (90 mL) at 0 °C were added dropwise TEA (11.4 g, 112 mmol), methanesulfonyl chloride (4.2 g, 35 mmol), and 4-DMAP (0.5 g, 4 mmol). The reaction mixture was warmed to room temperature and stirred overnight. The solution was filtered, the filter was washed with ether (50 mL), and the organic layer was concentrated in vacuo. The crude product was purified by flash chromatog-

(30) Collins, D. J.; James, A. M. *Aust. J. Chem.* **1989**, *42*, 223.

(31) Tanaka, Y.; Grapsas, I.; Dakoji, S.; Cho, Y.; Mobashery, S. *J. Am. Chem. Soc.* **1994**, *116*, 7475.

(32) Verdaguer, X.; Berk, S. C.; Buchwald, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 12641.

raphy (pentane/ethyl acetate: 95/5) to give **29** (1.5 g, 42%) as a colorless oil. IR (neat, cm^{-1}) 1662, 1091, and 700; ^1H NMR (300 MHz) δ 2.52 (2 H, t, J = 13.5 Hz), 3.43 (2 H, s), 4.36 (2 H, t, J = 15.1 Hz), 6.19 (1 H, s), and 7.29−7.41 (5 H, m); ^{13}C NMR (75.5 MHz) δ 140.9, 139.5, 128.4, 128.2, 125.9, 113.6, 69.9, 32.8, and 31.8; MS (EI) *m*/*z* (rel intensity) 160 (M^+, 75), 159 (19), 131 (97), 115 (38), 104 (47), 91 (100), and 51 (77). Anal. Calcd for $C_{11}H_{12}O$: C, 82.50; H, 7.50. Found: C, 82.59; H, 7.43.

3-Methyldihydrofuran-2-one (20). Following the procedure described for **21** without the use of HMPA, butyrolactone **9a** (5.2 g, 60 mmol) and methyl iodide (17.0 g, 120 mmol) gave **20** (4.0 g, 67%) as a colorless oil after flash chromatography (pentane/ethyl acetate: 3/1). All the physical and spectroscopic properties of the product were in complete agreement with the reported data.[33]

3-Methyltetrahydrofuran-2-ol (24). Following the procedure described for **13**, lactone **20** (4.5 g, 45 mmol) gave pure **24** (4.5 g, 98%) as a colorless oil. Physical and spectroscopic data of the product were in complete agreement with the literature data.[30]

4-Methyl-2,3-dihydrofuran (28). Following the procedure described for **14**, lactone **24** (4.5 g, 44 mmol) gave **28** (1.3 g, 35%) as a colorless oil. All the physical and spectroscopic data of the product were in complete agreement with the reported data.[15e]

3-Propyltetrahydropyran-2-one (22). Following the procedure described for **21**, valerolactone **9b** (4.4 g, 44 mmol) and propyl iodide (13.6 g, 80 mmol) gave **22** (1.4 g, 23%) as a colorless oil after distillation of the crude product (bp 132 °C, 18 mmHg). All the physical and spectroscopic data of the product were in complete agreement with the reported data.[18b]

3-Propyltetrahydropyran-2-ol (26). To a solution of lactone **22** (1.4 g, 10 mmol) in dry ether (25 mL) was added DIBALH (11 mL, 1 M solution in hexane, 11 mmol) at − 78 °C over 5 min. After additional stirring for 30 min, the reaction was quenched with methanol (5 mL) at − 78 °C. The resulting suspension was warmed to room temperature, and a saturated aqueous solution of Rochelle's salt (30 mL) was added. The resulting suspension was filtered through a pad of Celite, and the solids were washed carefully with ether. The filtrate was dried with $MgSO_4$ and concentrated in vacuo to give pure **26** (1.4 g, 98%) as a colorless oil. All the physical and spectroscopic data of the product were in complete agreement with the reported data.[18b]

5-Propyl-3,4-dihydropyran (30). Following the procedure described for **29**, alcohol **26** (0.7 g, 5 mmol) gave enol ether **30** (0.15 g, 24%) as a colorless oil after flash chromatography (pentane/ethyl acetate: 10/1). R_f 0.6 (pentane/ethyl acetate: 10/1); IR (neat, cm^{-1}) 1650, 1240, and 1070; ^1H NMR (300 MHz) δ 0.86 (3 H, t, J = 7.3 Hz), 1.30−1.45 (2 H, m), 1.78−1.95 (6 H, m), 3.87 (2 H, t, J = 5.6 Hz), and 6.21 (1 H, s); ^{13}C NMR (75.5 MHz) δ 138.7, 112.5, 65.2, 35.3, 22.9, 22.6, 20.9, and 13.6; MS (EI) *m*/*z* (rel intensity) 126 (M^+, 19), 97 (100), 69 (23), and 55 (26). Anal. Calcd for $C_8H_{14}O$: C, 76.19; H, 11.11. Found: C, 76.02; H, 11.26.

3-Benzyltetrahydropyran-2-one (23). Following the procedure described for **21**, valerolactone **9b** (4.4 g, 44 mmol) and benzyl bromide (13.7 g, 80 mmol) gave **23** (6.8 g, 82%) as a colorless oil after flash chromatography (pentane/ether: 2/1). All the physical and spectroscopic data of the product were in complete agreement with the reported data.[18b]

3-Benzyltetrahydropyran-2-ol (27). Following the procedure described for **26**, lactone **23** (2.7 g, 14 mmol) gave pure **27** (2.4 g, 90%) as a colorless oil. All the physical and spectroscopic data of the product were in complete agreement with the reported data.[18b]

5-Benzyl-3,4-dihydropyran (31). Following the procedure described for **29**, alcohol **27** (1.9 g, 10 mmol) gave pure enol ether **31** (1.1 g, 63%) as a colorless oil after flash chromatography (pentane/ether: 10/1). Physical and spectroscopic data of the product were in complete agreement with the literature values.[34]

6-Benzyl-3,4-dihydropyran (33). A mixture of 3,4-dihydropyran **8** (7.0 mL, 27.5 mmol) and TMEDA (1.0 g) was treated with *n*-BuLi (19.0 mL, 1.6 M solution in hexane, 30.3 mmol) over 5 min. Removal of the hexane afforded a white solid. A suspension of the dry lithium salt and dry ether (10 mL) was then treated with benzyl bromide (3.3 mL, 27.5 mmol) at 0 °C. After additional stirring for 1 h, the solution was washed with water (2 × 20 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography (pentane/ether: 98/2) to give **33** (3.4 g, 72%) as a slightly yellow oil. R_f 0.15 (pentane/ether: 98/2); IR (neat, cm^{-1}) 1674, 1061, and 700; ^1H NMR (300 MHz) δ 1.78−2.20 (4 H, m), 3.37 (2 H, s), 4.02 (2 H, t, J = 5.1 Hz), 4.57 (1 H, m), and 7.23−7.44 (5 H, m); ^{13}C NMR (75.5 MHz) δ 153.4, 138.6, 128.7, 128.1, 126.0, 97.1, 66.1, 40.7, 22.2, and 20.2; MS (EI) *m*/*z* (rel intensity) 174 (M^+, 28), 128 (8), 115 (16), 115 (16), 91 (90), 65 (55), and 55 (100). Anal. Calcd for $C_{12}H_{14}O$: C, 82.76; H, 8.05. Found: C, 82.75; H, 8.16.

Asymmetric Cyclopropanation of Enol Ethers 34a−i. General Procedure. In a dry 25 mL Schlenk tube under argon was dissolved $(CuOTf)_2 \cdot C_6H_6$ (5.1 mg, 0.010 mmol, 2.0 mol % Cu) in dry CH_2Cl_2 (2 mL) added with 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] **3** (7.1 mg, 0.024 mmol, 2.4 mol %) in dry CH_2Cl_2 (1 mL). The slightly yellow solution was stirred at room temperature for 30 min and then cooled to 0 °C. A solution of the enol ether (1 mmol) in dry CH_2Cl_2 (2 mL) was added to the copper complex. To the reaction mixture was added a solution of ethyl diazoacetate **6** (1.6 mmol) in CH_2Cl_2 (4 mL) dropwise over 7 h at 0 °C. After additional overnight stirring at room temperature, the reaction was quenched with saturated aqueous NH_4Cl (5 mL), diluted with ether (50 mL), washed with H_2O (5 mL) and brine (5 mL), and dried over $MgSO_4$. After concentration, the crude product was purified by flash chromatography (pentane/ethyl acetate: 95/5).

(1*SR*,5*SR*,6*SR*)-6-Carbethoxy-2-oxabicyclo[3.1.0]hexane (34a). The cyclopropanation reaction of 2,3-dihydrofuran **35** afforded cyclopropane **34a** (120 mg, 77%) as a colorless oil. R_f 0.23 (pentane/ethyl acetate: 95/5); IR (neat, cm^{-1}) 2981 and 1718; ^1H NMR (300 MHz) δ 1.16 (3 H, t, J = 7.2 Hz), 1.81−1.83 (1 H, m), 1.97−2.10 (3 H, m), 3.34−3.47 (1 H, m), 4.00 (2 H, q, J = 7.2 Hz), 4.10−4.19 (2 H, m); ^{13}C NMR (75.5 MHz) δ 172.1, 66.5, 65.5, 60.1, 27.4, 25.4, 23.0, and 14.0; MS (EI) *m*/*z* (rel intensity) 156 (M^+,13), 127 (25), 111 (19), 83 (100), and 55 (93). Anal. Calcd for $C_8H_{12}O_3$: C, 61.54; H, 7.69. Found: C, 61.38; H, 7.59.

(1*SR*,6*SR*,7*SR*)-7-Carbethoxy-2-oxabicyclo[4.1.0]heptane (34b). The cyclopropanation reaction of 3,4-dihydropyran **8** afforded the bicyclic product **34b** (131 mg, 77%) as a colorless oil. All the physical and spectroscopic data of the product were in complete agreement with the reported data.[16]

(1*R*,5*S*,6*S*)-5-Methyl-6-carbethoxy-2-oxabicyclo[3.1.0]-hexane (34c). Following the general procedure using enol ether **28** gave cyclopropane **34c** (102 mg, 60%) as a colorless oil. R_f 0.32 (pentane/ethyl acetate: 95/5); $[\alpha]^{25}_D = -4.9$ (c = 1.12, CH_2Cl_2, >95% ee); IR (neat, cm^{-1}) 1718, 1173, and 1098; ^1H NMR (300 MHz) δ 1.12 (3 H, t, J = 7.0 Hz), 1.20 (3 H, s), 1.96−2.13 (3 H, m), 3.42−3.49 (1 H, m), and 3.97−4.12 (4 H, m); ^{13}C NMR (75.5 MHz) δ 170.5, 69.8, 66.3, 60.2, 36.1, 32.7, 27.8, 14.3, and 12.4; MS (EI) *m*/*z* (rel intensity) 170 (M^+, <1), 141 (1), 125 (11), 97 (100), and 69 (27). Anal. Calcd for $C_9H_{14}O_3$: C, 63.53; H, 8.24. Found: C, 63.59; H, 8.37.

(1*R*,5*S*,6*S*)-5-Ethyl-6-carbethoxy-2-oxabicyclo[3.1.0]-hexane (34d). Following the general procedure using enol ether **14** gave cyclopropane **34d** (105 mg, 57%) as a colorless oil. R_f 0.28 (pentane/ethyl acetate: 95/5); $[\alpha]^{25}_D = -21.0$ (c = 1.00, CH_2Cl_2, >95% ee); IR (neat, cm^{-1}) 2967, 1718, 1174, and 1099; ^1H NMR (300 MHz) δ 0.90 (3 H, t, J = 7.5 Hz), 1.20 (3

(33) Ishii, Y.; Yoshida, T.; Yamawaki, K.; Ogawa, M. *J. Org. Chem.* **1988**, *53*, 5549.

(34) Barrett, A. G. M.; Betts, M. J.; Fenwick, A. *J. Org. Chem.* **1985**, *50*, 169.

H, t, $J = 7.2$ Hz), 1.61−2.15 (5 H, m), 3.42−3.51 (1 H, m), and 3.98−4.11 (4 H, m); ^{13}C NMR (75.5 MHz) δ 170.3, 69.6, 66.5, 60.1, 39.0, 33.3, 27.2, 20.2, 14.2, and 11.8; MS (EI) *m/z* (rel intensity) 184 (M^+, 1), 155 (9), 139 (20), 111 (100), 81 (28), and 55 (58). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.20; H, 8.70. Found: C, 64.93; H, 8.71.

(1*R*,5*R*,6*S*)-5-Benzyl-6-carbethoxy-2-oxabicyclo[3.1.0]-hexane (34e) and (1*R*,5*R*,6*R*)-5-Benzyl-6-carbethoxy-2-oxabicyclo[3.1.0]hexane (36). The cyclopropanation reaction of enol ether **29** afforded the bicyclic products **34e** (189 mg, 77%) and **36** in (49 mg, 20%) as colorless oils.

34e: R_f 0.28 (pentane/ethyl acetate: 95/5); $[\alpha]^{25}_D = -73.0$ ($c = 1.19$, CH_2Cl_2, >95% ee); IR (neat, cm^{-1}) 1715, 1417, 1178, and 1100; ^{1}H NMR (300 MHz) δ 1.25 (3 H, t, $J = 7.1$ Hz), 1.95−2.18 (3 H, m), 3.03 (1 H, d, $J = 14.9$ Hz), 3.24 (1 H, d, $J = 14.9$ Hz), 3.42−3.51 (1 H, m), 3.97−4.04 (1 H, m), 4.12 (2 H, q, $J = 7.1$ Hz), 4.31 (1 H, d, $J = 1.7$ Hz), 7.16−7.31 (5 H, m); ^{13}C NMR (75.5 MHz) δ 170.5, 139.4, 128.7, 126.1, 69.4, 66.4, 60.3, 38.2, 33.5, 32.7, 27.5, 14.2, and 11.8; MS (EI) *m/z* (rel intensity) 246 (M^+, 4), 173 (40), 155 (100), 127 (44), 115 (23), 91 (76), and 55 (51). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.17; H, 7.32. Found: C, 73.20; H, 7.45.

36: R_f 0.23 (pentane/ethyl acetate: 95/5); $[\alpha]^{25}_D = -54.2$ ($c = 0.50$, CH_2Cl_2, >95% ee); IR (neat, cm^{-1}) 2979, 1716, 1178 (film, cm^{-1}); ^{1}H NMR (300 MHz) δ 1.31 (3 H, t, $J = 7.1$ Hz), 1.68 (1 H, d, $J = 7.7$ Hz), 2.08−2.21 (1 H, m), 2.50−2.67 (1 H, m), 2.88−3.07 (2 H, m), 4.09 (1 H, d, $J = 7.7$ Hz), 4.16−4.22 (4 H, m), and 7.23−7.35 (5 H, m); ^{13}C NMR (75.5 MHz) δ 169.8, 138.2, 128.9, 128.5, 126.6, 74.2, 68.5, 60.1, 40.5, 37.5, 33.3, 29.9, and 14.2; MS (EI) *m/z* (rel intensity) 246 (M^+, 3), 173 (35), 155 (100), 127 (41), and 91 (79). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.17; H, 7.32. Found: C, 73.03; H, 7.36.

(1*R*,6*S*,7*S*)-6-Ethyl-7-carbethoxy-2-oxabicyclo[4.1.0]-heptane (34f). Following the general procedure using enol ether **19** gave cyclopropane **34f** (103 mg, 52%) as a colorless oil. R_f 0.21 (pentane/ethyl acetate: 95/5); $[\alpha]^{25}_D = -14.8$ ($c = 1.42$, CH_2Cl_2, >95% ee); IR (neat, cm^{-1}) 1721, 1158, and 1127; ^{1}H NMR (300 MHz) δ 0.86 (3 H, t, $J = 7.3$ Hz), 1.24 (3 H, t, $J = 7.2$ Hz), 1.45−1.81 (6 H, m), 2.07−2.15 (1 H, m), 3.24−3.32 (1 H, m), 3.56−3.61 (1 H, m), 3.80−3.84 (1 H, m), and 4.10 (2 H, q, $J = 7.3$ Hz); ^{13}C NMR (75.5 MHz) δ 171.4, 65.2, 64.2, 60.1, 33.3, 31.1, 25.4, 25.0, 21.9, 14.3, and 10.0; MS (EI) *m/z* (rel intensity) 198 (M^+, 3), 169 (51), 141 (36), 125 (100), and 95 (67). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.67; H, 9.10. Found: C, 66.75; H, 9.27.

(1*R*,6*S*,7*S*)-6-Propyl-7-carbethoxy-2-oxabicyclo[4.1.0]-heptane (34g). Following the general procedure using enol ether **30** gave cyclopropane **34g** (115 mg, 54%) as a colorless oil. R_f 0.14 (pentane/ethyl acetate: 95/5); $[\alpha]^{25}_D = +2.8$ ($c = 0.90$, CH_2Cl_2, >95% ee); IR (neat, cm^{-1}) 1716, 1307, 1180, and 1132; ^{1}H NMR (300 MHz) δ 0.83−1.75 (13 H, m), 1.92 (1 H, d, $J = 2.9$ Hz), 2.92−3.00 (1 H, m), 3.22−3.36 (2 H, m), 3.91−3.99 (2 H, m) and 4.11 (1 H, d, $J = 2.9$ Hz); ^{13}C NMR (75.5 MHz) δ 171.6, 65.5, 64.0, 60.0, 34.7, 32.1, 31.6, 25.7, 22.2, 19.5, 14.3, and 14.2; MS (EI) *m/z* (rel intensity) 183 (M^+-C_2H_5, 11), 169 (61), 139 (100), 123 (72), 95 (81), 67 (88), and 55(82). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.92; H, 9.43. Found: C, 67.71; H, 9.63.

(1*R*,6*R*,7*S*)-6-Benzyl-7-carbethoxy-2-oxabicyclo[4.1.0]-heptane (34h). Following the general procedure using enol ether **31** gave cyclopropane **34h** (174 mg, 67%) as a colorless oil. R_f 0.12 (pentane/ethyl acetate: 95/5); $[\alpha]^{25}_D = -31.7$ ($c = 2.50$, CH_2Cl_2, 96% ee); IR (neat, cm^{-1}) 1716 and 1123; ^{1}H NMR (300 MHz) δ 1.31 (3 H, t, $J = 7.1$ Hz), 1.46−1.51 (2 H, m), 1.74−1.85 (1 H, m), 1.93−1.98 (2 H, m), 2.90−3.07 (2 H, m), 3.22−3.31 (1 H, m), 3.60−3.65 (1 H, m), 4.16−4.24 (3 H, m), and 7.21−7.35 (5 H, m); ^{13}C NMR (75.5 MHz) δ 171.5, 138.8, 129.1, 128.3, 126.2, 64.9, 64.1, 60.4, 37.4, 32.7, 31.2, 25.0, 21.8, and 14.3; MS (EI) *m/z* (rel intensity) 260 (M^+, 1), 215 (6), 169 (100), 141 (55), 123 (31), and 65 (54). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.84; H, 7.69. Found: C, 73.94; H, 7.71.

(1*R,6*R**,7*R**)-1-Benzyl-7-carbethoxy-2-oxabicyclo[4.1.0]-heptane (34i).** Following the general procedure using enol ether **33** gave cyclopropane **34i** (117 mg, 45%) as a colorless oil. R_f 0.20 (pentane/ethyl acetate: 95/5); IR (neat, cm^{-1}) 2981, 2936, 1720, and 1298; ^{1}H NMR (300 MHz) δ 1.31 (3 H, t, $J = 7.1$ Hz), 1.78−2.12 (4 H, m), 2.87−3.11 (3 H, m), 3.52 (1 H, d, $J = 10.7$ Hz), 4.07−4.15 (2 H, m), 4.24 (2 H, q, $J = 7.1$ Hz), and 7.18−7.29 (5 H, m); ^{13}C NMR (75.5 MHz) δ 171.8, 138.7, 133.6, 129.3, 128.1, 68.1, 64.7, 61.3, 37.9, 31.3, 26.4, 21.0, 19.1, and 14.2; MS (EI) *m/z* (rel intensity) 260 (M^+, 7), 231 (3), 185 (13), 115 (10), 91 (100), and 65 (35). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.84; H, 7.69. Found: C, 73.85; H, 7.64.

Determination of the Enantiomeric Excess via Alcohol Derivatives. (1*R,6*R**,7*R**)-1-Benzyl-7-(hydroxymethyl)-2-oxabicyclo[4.1.0]heptane (39).** Ester **34i** (260 mg, 1 mmol) in dry ether (5 mL) was added over 5 min to an ice-cooled suspension of $LiAlH_4$ (76 mg, 2 mmol) in ether (25 mL). After stirring overnight at room temperature, H_2O (1 mL) was added. The suspension was filtered, dried over $MgSO_4$, and concentrated. The residue was purified by using flash chromatography (pentane/ethyl acetate: 2/1) to afford **39** (180 mg, 82%) as a colorless oil. R_f 0.15 (pentane/ethyl acetate: 2/1); $[\alpha]^{25}_D = +14.8$ ($c = 1.00$, CH_2Cl_2, 74% ee); IR (neat, cm^{-1}) 3383, 2929, 1078, and 706; ^{1}H NMR (300 MHz) δ 0.93 (1 H, t, $J = 6.2$ Hz), 1.22−1.29 (3 H, m), 1.61−1.78 (1 H, m), 1.80−1.91 (1 H, m), 2.03 (1 H, s), 2.66−2.77 (2 H, m), 2.92 (1 H, d, $J = 14.6$ Hz), 3.37−3.63 (3 H, m), and 7.12−7.29 (5 H, m); ^{13}C NMR (75.5 MHz) δ 139.1, 129.1, 128.1, 126.1, 64.2, 63.2, 63.1, 39.8, 30.8, 21.7, 21.5, and 19.5; MS (EI) *m/z* (rel intensity) 200 ($M^+ - H_2O$, 18), 129 (14), 91 (100), 65 (69), and 53 (67). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.06; H, 8.26. Found: C, 77.29; H, 8.30.

(1*R*,5*S*,6*R*)-5-Benzyl-6-(hydroxymethyl)-2-oxabicyclo-[3.1.0]hexane (37). Following the procedure described for **39**, ester **34e** (300 mg, 1.2 mmol) gave **37** (218 mg, 85%) as a colorless oil after flash chromatography (pentane/ethyl acetate: 2/1). R_f 0.18 (pentane/ethyl acetate: 2/1); $[\alpha]^{25}_D = -10.1$ ($c = 1.00$, CH_2Cl_2, 96% ee); IR (neat, cm^{-1}) 3419; ^{1}H NMR (300 MHz) δ 1.62−1.90 (2 H, m), 2.00−2.20 (2 H, m), 3.00−3.07 (2 H, m), 3.56−3.81 (3 H, m), 3.99−4.06 (1 H, m), and 7.26−7.39 (5 H, m); ^{13}C NMR (75.5 MHz) δ 139.8, 128.7, 128.5, 126.2, 67.4, 66.4, 60.4, 35.1, 33.9, 31.8, and 28.2; MS (EI) *m/z* (rel intensity) 173 ($M^+ - CH_2OH$, 24), 129 (24), 115 (20), 91 (100), and 65 (54). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.47; H, 7.84. Found: C, 76.48; H, 7.99.

(1*R*,6*S*,7*R*)-6-Benzyl-7-(hydroxymethyl)-2-oxabicyclo-[4.1.0]heptane (38). Following the procedure described for **39**, ester **34h** (260 mg, 1.0 mmol) gave **38** (183 mg, 84%) as a colorless oil after flash chromatography (pentane/ethyl acetate: 2/1). R_f 0.09 (pentane/ethyl acetate: 2/1); $[\alpha]^{25}_D = +22.2$ ($c = 1.00$, CH_2Cl_2, 96% ee); IR (neat, cm^{-1}) 3393, 2933, and 1136; ^{1}H NMR (300 MHz) δ 1.23−1.27 (1 H, m), 1.36−1.47 (3 H, m), 1.69−1.73 (1 H, m), 1.88−1.94 (1 H, m), 2.05−2.31 (2H, m), 3.16−3.24 (1 H, m), 3.51−3.62 (2 H, m), 3.72−3.85 (2 H, m), and 7.24−7.38 (5 H, m); ^{13}C NMR (75.5 MHz) δ 139.2, 129.1, 128.4, 126.2, 64.2, 61.9, 61.3, 39.4, 31.0, 25.1, 25.0, and 21.8; MS (EI) *m/z* (rel intensity) 187 ($M^+ - CH_2OH$, 5), 127 (28), 115 (18), 91 (100), and 65 (40). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.06; H, 8.26. Found: C, 76.92; H, 8.41.

Synthesis of (+)-Quebrachamine (7). Determination of the Absolute Configuration of the Asymmetric Cyclopropanation Products (34c−h). (3a*S*,7a*R*)-3a-Ethyltetrahydrofuro[2,3-b]pyran-2-one (40). A solution of ester **34f** (580 mg, 2.9 mmol) and 10% H_2SO_4 (11.6 mL) in dioxane (5.8 mL) was refluxed for 15 h. The dioxane was removed in vacuo, and the residue was treated with brine (5 mL) and extracted with ether (4 × 25 mL). The extracts were washed with brine (5 mL) and saturated aqueous $NaHCO_3$ (5 mL), dried over $MgSO_4$, and concentrated in vacuo to give **40** (380 mg, 77%) as a colorless oil which was used in the next step without purification. R_f 0.44 (pentane/ethyl acetate: 3/1); $[\alpha]^{25}_D = -21.7$ ($c = 1.00$, CH_2Cl_2); IR (neat, cm^{-1}) 1787, 1190, 1165, and 919; ^{1}H NMR (300 MHz) δ 0.90 (3 H, t, $J = 7.6$ Hz), 1.44−1.75 (6 H, m), 2.31 (1 H, d, $J = 16.9$ Hz), 2.37 (1 H, d, $J = 16.9$ Hz), 3.65−3.72 (1 H, m), 3.80−3.86 (1 H, m), and 5.30 (1 H, s); ^{13}C NMR (75.5 MHz) δ 174.0, 105.2, 67.0, 62.1, 40.6, 40.0, 27.3, 27.0, 20.0, and 8.5; MS (EI) *m/z* (rel intensity) 154 (4), 125 (17), 97 (85), 69 (55), and 55 (100). Anal. Calcd for $C_9H_{14}O_3$: C, 63.53; H, 8.23. Found: C, 63.75; H, 8.18.

(3a*S*,7a*R*)-3a-Ethylhexahydrofuro[2,3-b]pyran-2-ol (41). To a solution of lactone **40** (250 mg, 1.5 mmol) in dry ether (5 mL) was introduced dropwise DIBALH (1.6 mL, 1 M solution in hexane, 1.6 mmol) over 5 min at − 78 °C. After additional stirring for 1 h at this temperature, the reaction mixture was slowly warmed to room temperature. The reaction was quenched with 1 M HCl (5 mL) and extracted with ether (4 × 5 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (5 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified via flash chromatography (pentane/ethyl acetate: 1/1) to give pure acetal **41** (217 mg, 79%) as an unseparable mixture of cis and trans diastereomers. R_f 0.18 (pentane/ethyl acetate: 1/1); $[\alpha]^{25}_D$ = +12.2 (c = 1.00, CH_2Cl_2); IR (neat, cm^{-1}) 3416, 2939, 2880, and 1463; ^{1}H NMR (300 MHz) δ 0.90 (6 H, m), 1.31−2.13 (16 H, m), 3.34−3.38 (1 H, m), 3.48−3.57 (1 H, m), 3.77−3.86 (1 H, m), 3.90−3.98 (2 H, m), 4.12−4.21 (1 H, m), 4.69 (1 H, s), 5.02 (1 H, s), and 5.53−5.68 (2 H, m); ^{13}C NMR (75.5 MHz) δ 105.6, 105.1, 100.0, 97.0, 64.3, 61.7, 44.9, 41.9, 41.1, 38.7, 30.5, 28.1, 27.9, 27.5, 21.1, 20.6, 8.5, and 7.8; MS (EI) m/z (rel intensity) 171 ($M^+ - 1$, 1), 154 ($M^+ - H_2O$, 4), 125 (13), 97 (100), 85 (44), and 69 (60). Anal. Calcd for $C_9H_{16}O_3$: C, 62.79; H, 9.30. Found: C, 62.71; H, 9.43.

(2*S*,4*RS*)-3-(2-Ethyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indol-2-yl)propan-1-ol (42). Alcohol **41** (467 mg, 2.7 mmol) was stirred with tryptamine hydrochloride (800 mg, 4.1 mmol) in 10% aqueous acetic acid (5 mL) for 7 h at room temperature under N_2. After the addition of 150 mg of sodium acetate, the reaction mixture was stirred for another 44 h. The solution was treated with 10% aqueous Na_2CO_3 until pH > 7 and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried over $MgSO_4$ and passed through a short column of neutral alumina to give a yellow foam (832 mg) after concentration in vacuo. The foam was treated directly with $NaBH_3CN$ (210 mg, 3.3 mmol) in 10% aqueous acetic acid (10 mL). After stirring for 20 min at room temperature, the solution was extracted with CH_2Cl_2 (3 × 10 mL), and the combined extracts were dried over $MgSO_4$ and concentrated to give **42** (728 mg, 90%) as a mixture of diastereomers. All physical and spectroscopic data of the product were in complete agreement with the literature values.[26a]

(*11*S)-11-Ethyl-5,8,9,10,11,12,13,14-octahydro-6*H*-7,14-diaza-7,11-methanocycloundeca[α]indene ((+)-Quebrachamine) (7). The diastereomeric mixture of **42** (210 mg, 0.7 mmol) was dissolved in a mixture of dry TEA (2.5 mL) and $CHCl_3$ (5 mL) and cooled to − 10 °C. To this stirred solution was then introduced dropwise via a syringe methanesulfonyl chloride (500 mg, 4.4 mmol). When the addition was complete, the reaction mixture was stirred for 40 h at room temperature. Concentration in vacuo gave a brown oil which was directly dissolved in dry *N*-methylmorpholine (50 mL) and treated portionwise with $LiAlH_4$ (800 mg, 21.1 mmol). The resulting suspension was heated at reflux for 13 h and then carefully treated dropwise with water (5 mL) at 0 °C. After filtration through a pad of Celite and concentration in vacuo the crude product was purified by flash chromatography on neutral activated alumina (pentane/ethyl acetate: 10/1) and recrystallized from methanol to give **7** (138 mg, 67%) as white crystals. $[\alpha]^{22}_D$ = +111 (c = 0.18, $CHCl_3$) (lit.[28] $[\alpha]^{22}_D$ = +117, c = 0.18, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.88 (3 H, t, J = 7.5 Hz), 1.10−1.35 (5 H, m), 1.50−1.64 (3 H, m), 1.85−2.01 (1 H, m), 2.21−2.48 (4 H, m), 2.69−2.95 (4 H, m), 3.27 (1 H, d, J = 11.9 Hz), 7.09−7.13 (2 H, m), 7.26−7.30 (1 H, m), 7.50−7.53 (1 H, m), and 7.69 (1 H, s); ^{13}C NMR (75.5 MHz) δ 139.7, 134.7, 128.9, 120.1, 118.6, 117.4, 110.0, 108.7, 56.7, 55.1, 53.4, 53.2, 37.1, 34.7, 33.4, 32.0, 22.7, 22.4, 21.9, and 7.8. All other physical and spectroscopic data of the product were also in complete agreement with the reported data.[27]

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