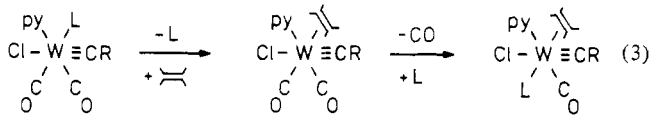
ligands trans to the carbyne and the alkene, respectively, and the pyridine ligand trans to carbon monoxide are obtained.[12,13]

The neutral complex $Cl(CO)_2(py)_2W{\equiv}CPh$ (**1**) reacts with maleic anhydride and fumaronitrile in THF to afford the neutral complexes $Cl(py)_2(CO)(alkene)W{\equiv}CPh$, **9** and **10** (**9**, alkene = maleic anhydride; **10**, alkene = fumaronitrile), in 70–90% yield.[14] Complex **1** is significantly less reactive than its anionic counterpart **3**. A large excess (10 equiv) of the alkenes and slightly elevated temperatures (40–50 °C) are required for this reaction to proceed at convenient rates.

The molecular structure of the maleic anhydride complex **9** is shown in Figure 1.[15] It is that expected[16] for a chloro tungsten carbyne complex containing two donor ligands (py) and two acceptor ligands (maleic anhydride and carbon monoxide) with the chloride trans to the carbyne and the pyridine ligands trans to maleic anhydride and CO. The alkene double bond is perpendicular relative to the tungsten–carbyne bond[17] thus maximizing π-bonding to the metal of both the alkene and the carbyne ligand. The anhydride group of maleic anhydride is oriented toward the carbyne ligand.

The most surprising feature in the reactions leading to the tungsten alkene carbyne complexes is the facile loss of carbon monoxide—normally, substitution of a carbonyl ligand in bis-substituted tungsten carbyne complexes $X(CO)_2(L)_2W{\equiv}CR$ is difficult.[18] Therefore, we postulate an indirect mechanism for the substitution of carbon monoxide (eq 3). In the first step one



(3)

of the donor ligands (L = Cl^-, py) is substituted by the alkene ligand affording a neutral intermediate with the alkene ligand trans to one of the two carbon monoxide ligands. Subsequently, the CO trans to the strongly π-bonding alkene is labilized and substituted by the ligand L (L = Cl^-, py) giving rise to the observed products. Faster reaction of the anionic complexes **3** and **4** over the neutral complex **1** indicates that the first step is rate-determining. Lack of reaction of unactivated alkenes may be associated with the second step. Labilization of CO apparently is only achieved by electron-poor olefins such as maleic anhydride or fumaronitrile.

Acknowledgment. This work was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and by the National Science Foundation (CHE-8411023).

Supplementary Material Available: Crystallographic data for 9: atomic coordinates (Table 1S), bond distances (Table 2S), bond angles (Table 3S), anisotropic temperature factors (Table 4S), hydrogen atom coordinates (Table 5S), and observed vs. calculated structure factors (Table 6S) (23 page). Ordering information is given on any current masthead page.

(11) Elemental analyses have been obtained for the new tungsten complexes **5–10**.

(12) The cis arrangement of the alkene and pyridine ligands in **5–8** is confirmed by NOE difference spectroscopy. Irradiation of an NMR sample of **5** at the resonance frequency of the pyridine α-protons at 9.43 ppm leads to an increase in intensity of the alkene proton signal at 2.93 ppm.

(13) The fumaronitrile complexes **7** and **8** as well as **10** are obtained as mixtures of diastereomers (approximately 1:1) due to coordination of the enantiotopic faces of fumaronitrile to the asymmetric complex fragments $Cl(CO)(py)(L)W{\equiv}CR$ in **7** and **8** (L = Cl^-) as well as **10** (L = py).

(14) **9**: IR (cm^{-1}, CH_2Cl_2) ν_{CO} 2044 (s), $\nu_{C=O}$ 1806 (s), 1738 (s); ^1H NMR (ppm, $CDCl_3$) 4.42 (d), 3.19 (d) (J = 5.3 Hz) (CH=CH); ^{13}C NMR (ppm, $CDCl_3$) 268.0 (*C*Ph), 207.1 (CO), 175.3, 173.4 (C=O), 55.4 (d, J_{CH} = 180 Hz), 51.8 (d, J_{CH} = 177 Hz) (C=C). **10**: Two diastereomers; IR (cm^{-1}, CH_2Cl_2) ν_{CN} 2218 (m), ν_{CO} 2049 (s); ^1H NMR (ppm, $CDCl_3$) 3.41 (d), 3.32 (d) (J = 9.2 Hz), 3.36 (d), 2.39 (J = 9.2 Hz) (CH=CH); ^{13}C NMR (ppm, $CDCl_3$) 264.7, 264.3 (*C*Ph), 208.2, 206.7 (CO), 35.4, 33.7, 32.6, 30.0 (C=C).

(15) $Cl(CO)$(maleic anhydride)$(py)_2W{\equiv}CPh$ (**9**, monoclinic, $P2_1/n$, a = 11.522 Å (2) b = 16.026 (3) Å, c = 11.680 (2) Å, β = 102.97 (1)°, V = 2101.7 (6) Å^3, Z = 4, μ(Mo Kα) = 59.8 cm^{-1}, ρ(calcd) = 1.87 g cm^{-3}, T = 23 °C. Of 4045 absorption corrected reflections collected, $4° \geq 2\theta \geq 50°$, 3698 were unique and 3218 with $F_o \geq 3\sigma(F_o)$ were used in the solution (heavy atom) and refinement (blocked cascade) of the structure. All non-hydrogen atoms anisotropic, hydrogen atoms idealized. R_F = 3.28%; R_{wF} = 3.56%; GOF = 1.51; highest peak, final difference map, 0.98 e Å^{-3} (1.01 Å from W).

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(17) Orthogonal bonding arrangement of an alkene and a metal–carbon triple bond was also observed in $W(CAl_2Me_4Cl)(PMe_3)_2(CH_3)(C_2H_4)$. Churchill, M. R.; Wasserman, H. J. *Inorg. Chem.* **1981**, *20*, 4119–4123.

(18) Unpublished observations.

Efficient Asymmetric Synthesis of (+)-Mesembrine and Related Chiral 4,4-Disubstituted Cyclohexanones

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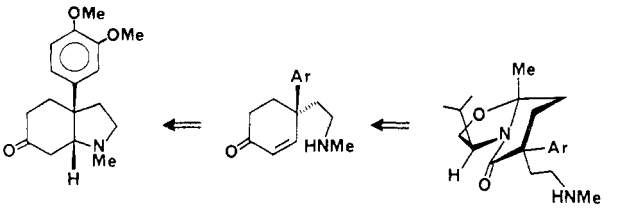
In spite of the numerous racemic total syntheses[1] of the *Sceletium* alkaloid mesembrine **1**, there is yet to be described in the literature a true asymmetric approach to this substance. In 1973 Yamada and Otani[2] reported a synthesis enriched in the (+) enantiomer of **1** in 25–30% ee via an optically active proline derivative and more recently Takano[3] reported an enantioselective synthesis of naturally occurring (−)-mesembrine. However, the latter work, originating from D-mannitol, was of an indirect nature wherein none of the stereocenters of mannitol were carried through to the final product. Instead a chiral intermediate was prepared, which was brought forward to the target via well-known procedures. Our recent interest[4,5] in asymmetric synthesis of compounds containing quaternary carbon centers with specific stereochemistry has led us to consider mesembrine as a viable target via 4,4-disubstituted cyclohexanones **2**, which could be derived from the



(+)-**1** **2**, Ar = 3,4-$(MeO)_2$Ph **3**

chiral, nonracemic, bicyclic lactam **3**. Previously we described the synthetic value of the [3.3.0]-bicyclic lactams **4** and **5** as precursors to 2,2-disubstituted keto acids **7**[4] and 4,4-disubstituted cyclopentenones **8**[5] by sequential alkylation to the bicyclic lactams **6** in very high enantiomeric purity (Scheme I).

We now report that it is feasible to prepare [4.3.0]-bicyclic lactams and sequentially alkylate them to the key intermediate **3** which led to an efficient synthesis of (+)-mesembrine in 23% overall yield and in >98% enantiomeric excess.

The requisite keto acid (±)-**9** was prepared from the dilithio salt of (3,4-dimethoxyphenyl)acetic acid and 2-methyl-2-(2-iodoethyl)-1,3-dioxolane[6] (2 equiv of BuLi, 0–30 °C, THF) and acidified (EtOH, pyridinium–TsOH, 60 °C) to cleave the ketal furnishing **9** in 85% yield (mp 72–74 °C). Treatment of (±)-**9**

(1) The synthesis of (±)-mesembrine has been described by a number of laboratories: Kochhar, K. S.; Pinnick, H. W. *Tetrahedron Lett.* **1983**, *24*, 4785. A complete bibliography for previous syntheses is given therein.

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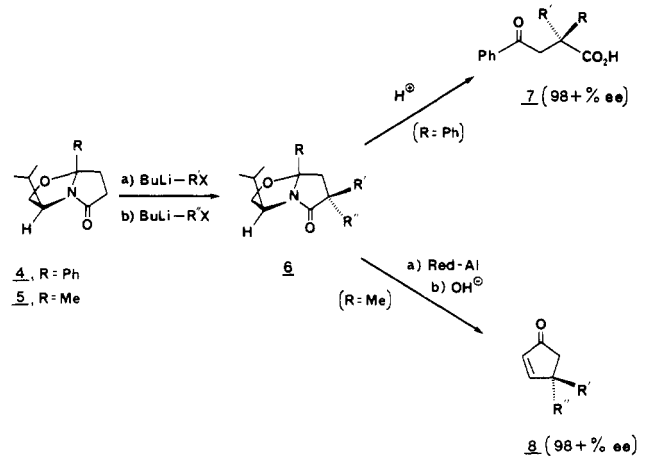
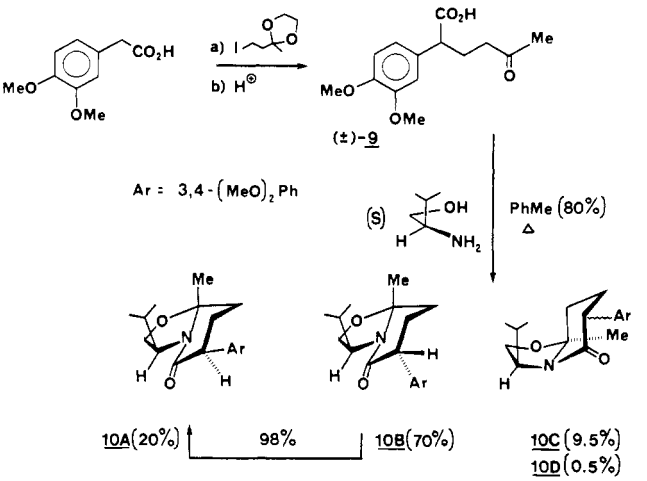
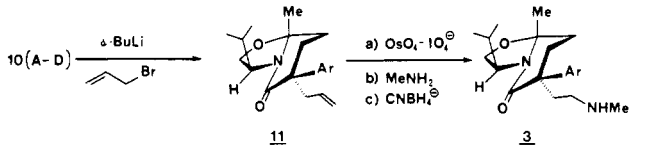
Scheme I

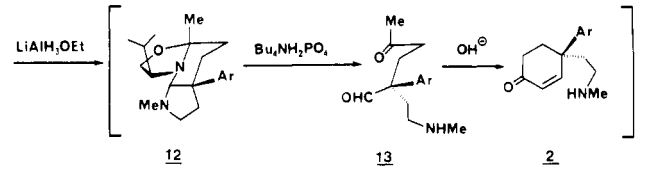


with (*S*)-valinol in toluene[7] and heating to reflux for 16 h produced the bicyclic lactam **10** as a mixture of diastereomers (**10A**, 20%, **10B**, 70%, **10C**, 9.5%, **10D**, <0.5%).[8] The major products **10A,B**



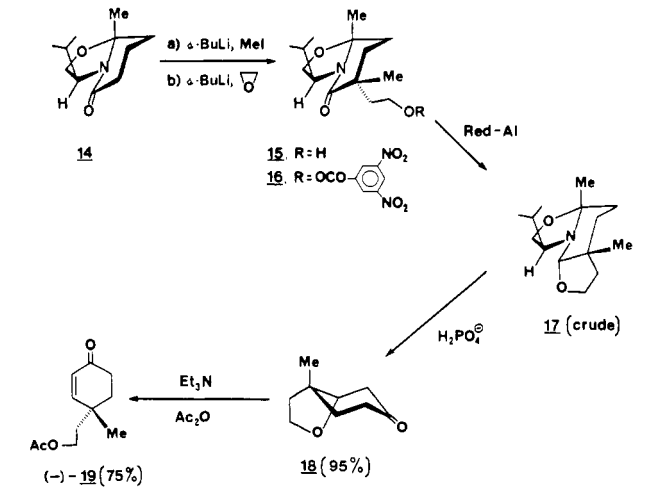
were found, after separation by flash chromatography or peak matching from HPLC, to be identical except at the C–aryl bond. However, metalation and kinetic protonation (2 equiv of *s*-BuLi, -78 °C, H_2O or D_2O) transformed **10B** quantitatively to **10A**.[9] The minor isomers **10C** and **10D** were shown[9] to be epimeric with **10A,B** at the angular methyl group. With this information in hand, at least 90% of the bicyclic lactams **10** are useful for the mesembrine synthesis since the enolate derived from **10A,B** would be identical. Rather than separate the four-component mixture (**10A–D**), the mixture was metalated (2 equiv of *s*-BuLi, THF, –20 °C) and treated with allyl bromide (2.2 equiv, –10 °C) to give the alkylated product **11** (90%) along with 10% material originating from **10C,D**. The latter minor components were readily separated (silica gel, hexane–EtOAc) to furnish pure **11** in 71% yield starting from the mixture **10A–D**. Thus, the alkylation of **10A,B** proceeded with >99% diastereoselection from the endo face while the only contaminants were those derived from **10C,D**. The allyl group in **11** was transformed into the aminoethyl group **3**, in 72% yield, by Lemieux oxidation (0.05 equiv of OsO_4, 3.0 equiv of $NaIO_4$, ether, water, 8 h, 25 °C), affording initially the crude aldehyde which was immediately subjected to reductive amination.[10] When **10A,B** (free of **10C,D**) was alkylated with *N*-carboethoxy(2-bromoethyl)methylamine and then decarboxylated, so as to produce **3** in a more direct manner, diastereomeric ratios of **3** were found to be only 4:1 (HPLC) in favor of endo alkylation. However, HPLC analyses of **3** derived from the allyl derivative showed complete absence of any other diastereomers. The asymmetric synthesis of (+)-**1** was completed by reduction of **3** using $LiAl(OEt)H_3$ in dimethoxyethane–toluene at –20 °C, affording the tricyclic product **12**. Without purification, **12** was heated with an ethanolic solution of tetrabutylammonium dihydrogen phosphate to furnish the keto aldehyde **13** and once again, without purification, treated at room temperature with 4 N NaOH to cyclize to **2** and spontaneously to (+)-**1**. Purification





(radial chromatography, silica gel, THF–hexane–Et_3N, 10:10:1) gave enantiomerically pure (+)-**1** in 60% yield from **3**: $[\alpha]_D$ 58.5° (*c* 0.04, MeOH), lit. –55.4°,[11a] –59.0°[11b] (MeOH) for the natural enantiomer.[12] The product was identical in all respects when compared to (±)-**1**.[10] The acquisition of (+)-**1** also confirms the absolute stereochemistry in **11**. Although not performed, it is expected that (*R*)-valinol would lead, in this sequence, to natural (–)-mesembrine.

This process was also extended to another chiral cyclohexenone by alkylation of the bicyclic lactam **14** (from 5-ketohexanoic acid, (*S*)-valinol, *p*-TsOH, toluene, 65%) with *sec*-butyllithium and methyl iodide (–78 °C, THF). The ratio of 2-methyl products was only 3:1 (90% yield). However, in view of the second alkylation via the enolate, the poor ratio was again of no consequence. Metalation with 1.1 equiv of *sec*-butyllithium (–78 °C, THF) followed by ethylene oxide (1.5 equiv, –78 to –20 °C) gave **15** as an 86:14 mixture of endo–exo diastereomers. Confirmation of the endo alkylation as the major path was achieved by a single-crystal X-ray study on the 3,5-dinitrobenzoate **16**. Flash



(7) Optimum conditions for the formation of **10** required that the keto acid **9** be 0.04 M in toluene. Higher concentrations resulted in side products and lower yields. Acid catalysis was also avoided due to side product formation.

(8) The ratios for **10A–D** were determined by HPLC; Zorbax column, hexane–EtOAc, 2:3.

(9) The relative stereochemistry of **10A,B** was determined by single-crystal X-ray study and since the valinol was known to be *S*, the 2-carbon substituents are also known. ^1H NMR was also utilized to assign stereochemistry in a wide variety of alkylated lactams. These will be described in our full paper.

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(12) The absolute configuration of (+)-mesembrine has been assigned from ORD studies by Otani and Yamada.[2]

chromatography (silica gel, CH_2Cl_2–THF 85:15) separated pure **15** from its *exo*-hydroxyethyl epimer. Removal of the chiral auxiliary was accomplished using Red-Al in toluene (−60 to −20 °C) followed by heating the crude tricyclic aminal **17** with ethanolic $Bu_4NH_2PO_4$ for 20 h. In this manner the bicyclic ketone **18** was isolated, after flash chromatography (ether, silica in 94.7% yield from **15**. Furthermore, treatment of **18** with 8.0 equiv of Et_3N, 4.0 equiv of acetic anhydride in THF, and heating for 4 days gave (*R*)-(−)-4-methyl-4-(acetoxyethyl)-2-cyclohexanone (**19**), $[\alpha]^{25}_D$ −28.42°, in 75% yield. The absolute configuration was derived from the X-ray structure of **16**.

The above demonstrates the utility of these bicyclic lactams (**4, 5, 10, 14**) as chiral precursors to various 4-substituted cyclopentenones and cyclohexenones in high enantiomeric purity. Additional aspects of this class of compounds are under investigation and will be reported in the near future.

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Supplementary Material Available: Physical data for all compounds, 270-MHz spectra for (+)- and (±)-mesembrine and X-ray structure of 16 (7 pages). Ordering information is given on any current masthead page.

Time Reversal of the Evolution under Scalar Spin–Spin Interactions in NMR. Application for ω_1 Decoupling in Two-Dimensional NOE Spectroscopy

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It is known that two-dimensional (2D) NMR[1] is accessible to numerous manipulations which can significantly enhance its power for the analysis of complex molecules. In this context, it is frequently desirable to simplify 2D spectra by eliminating the effects of scalar spin–spin couplings during the evolution period in order to achieve homonuclear decoupling in the ω_1 frequency dimension. The only technique so far available for this purpose, the constant-time experiment proposed by Bax and Freeman,[2,3] suffers from a strong dependence of the signal intensities on relaxation times and J coupling constants.

In this paper we introduce a new concept which allows time reversal (TR) of the evolution under scalar spin–spin interactions leading to homonuclear decoupling without the disadvantages of constant-time experiments. The basic principle relies on the different dependencies of the various coherence transfer pathways on the rotation angle β of a TR rotation introduced at a suitable place. The TR element effects a unique selection of those pathways that involve time reversal of the J evolution.

The condition for time reversal can easily be formulated in terms of spin multiplet components expressed by product operators. In the case of a three-spin system we encounter for example the operator $I_1^+I_2^\alpha I_3^\beta$, signifying a single-quantum coherence of spin I_1 with the coupling partners I_2 and I_3 in their α and β states, respectively. Time reversal of the J evolution is achieved if the TR element inverts all passive spins (I_2, I_3) while leaving the active spin (I_1) unaffected: $I_1^+I_2^\alpha I_3^\beta \rightarrow I_1^+I_2^\beta I_3^\alpha$. No single nonselective rotation exists that fulfills this requirement. However, the desired effect can be achieved by combining experiments obtained with a pulse of variable rotation angle β selecting the proper dependence on β which is given by $\cos^2(\beta/2)\sin^4(\beta/2)$ in the above case. The basic principles are closely related to those of the recently introduced E.COSY technique.[4,5]

In the following, we insert the TR element in the middle of the evolution period t_1 of the pulse sequence for 2D NOE spectroscopy (NOESY).[6-9] The single TR pulse with flip angle β and phase ϕ is replaced for experimental convenience by an equivalent pair of 90° pulses, $90°(\beta+\phi)$–$90°(\pi+\phi)$. The entire pulse sequence for the NOESY TR experiment is then

$$90°(\beta+\Psi_1)\text{–}{}^1/_2t_1\text{–}\{90°(\beta+\phi)-90°(\pi+\phi)\}-{}^1/_2t_1\text{–}90°(0)\text{–}\tau_m\text{–}90°(\Psi_2)\text{–acq}(\Psi_1+\Psi_2)$$

The phase cycle for β is determined by the maximum number $N-1$ of coupling partners of any relevant spin in the sample. The phase β should be cycled in increments of π/N, $\beta_j = j\pi/N$ (j = 0, 1, ..., $N-1$, $N+1$, ..., $2N-1$) with the following weight factors[10] for the individual experiments:[11] $W_j = (N/8)(-1)^{j+N}\{\cos({}^1/_2\beta_j)\}^{-2}$.

The $90°(\beta+\phi)$–$90°(\pi+\phi)$ pulse pair may also be regarded as a multiple quantum filter.[12,13] The described phase cycle is then equivalent to a combination of p-quantum-filtered spectra with the weights $((-1)^p/12)(3p^2 - N^2 - {}^1/_2)$ for $0 \le p \le N$.

The above phase cycle for β selects the coherence transfer pathways[14] with Δp even of which only $\Delta p = 0$ leads to refocusing of the scalar interactions. It is therefore essential to select $\Delta p = 0$ by an additional phase cycle of the entire TR element. This is achieved by the three-step cycle $\phi = 0, 2\pi/3, 4\pi/3$.

The phases Ψ_1 and Ψ_2 are cycled to suppress axial peaks ($\Psi_1 = 0, \pi$) and single-quantum coherence during τ_m ($\Psi_2 = 0, \pi$), respectively. Zero-quantum suppression, a well-known problem in conventional NOESY,[15] is superfluous using NOESY TR due to the refocusing of the J interactions. The TPPI method[14,16] can be applied to the first pulse as usual for separating positive and negative frequencies and for obtaining pure 2D absorption line shapes.

Two potential drawbacks of the NOESY TR experiment should be mentioned. (1) In comparison to conventional NOESY, a sensitivity loss of about a factor 2.5 (depending on N) has to be taken into account, comparing the intensity of the singlet in the ω_1 dimension of the NOESY TR spectrum with the intensity of a non-degenerate multiplet component in the corresponding conventional NOESY spectrum. (2) Additional, undesired cross peaks centered at the positions $(\omega_1, \omega_2) = ({}^1/_2[\Omega_k + \Omega_l], \Omega_m)$ can occur in systems of coupled spins. Spin I_m can either belong to the same spin system as I_k and I_l or may show cross relaxation to I_k or I_l. These peaks are, however, easily distinguished from the desired ω_1-decoupled peaks because they exhibit an antiphase

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