Enantioselective Synthesis of Functionalized Tropanes by Rhodium(II) Carboxylate-Catalyzed Decomposition of Vinyldiazomethanes in the Presence of Pyrroles

Huw M. L. Davies,*[,†] Julius J. Matasi,[†] L. Mark Hodges,[†] Nicholas J. S. Huby,[‡] Craig Thornley,[‡,§] Norman Kong,[†] and Jeffrey H. Houser[†]

Department of Chemistry, State University of New York at Buffalo Buffalo, New York 14260-3000 and Department of Chemistry, Wake Forest University Box 7486, Winston-Salem, North Carolina 27109

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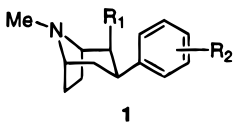
A series of enantiomerically enriched tropanes was synthesized by the rhodium(II) octanoate-catalyzed reaction of various *N*-BOC-protected pyrroles with vinyldiazomethanes. The overall 3 + 4 annulation occurs by a tandem cyclopropanation/Cope rearrangement. Asymmetric induction was best achieved in these transformations by using either (*S*)-lactate or (*R*)-pantolactone as a chiral auxiliary on the vinyldiazomethanes. Reactions carried out with the chiral catalyst tetrakis-[*N*-(4-*tert*-butylbenzenesulfonyl)-(*L*)-prolinato]dirhodium (**2**) provided moderate asymmetric induction, but also resulted in the formation of isomeric azabicyclooctane side products. The utility of the synthetic process was demonstrated through the asymmetric synthesis of (−)-anhydroecgonine methyl ester and (−)-ferruginine.

Introduction

The tropane nucleus is found in numerous naturally occurring alkaloids, many of which possess potent biological activity.[1] Of particular current interest are the 2β-substituted-3β-aryltropanes **1**, as these compounds are useful probes to study the neurochemistry of drug addiction.[2] A number of classic methods have been developed for the construction of the tropane system,[3] and three asymmetric routes to tropanes have been reported within the last two years.[4] Even so, the most commonly employed procedure for the synthesis of the 2β-substituted-3β-aryltropanes has been through conjugate addition of aryl Grignard reagents to anhydroecgonine methyl ester,[2c−h] which is synthesized from (−)-cocaine.[5] We have shown that the 2β-acyl-3β-aryltropanes display very promising biological activity,[2a,b] and consequently, we required a practical asymmetric approach to these compounds that can be carried out on a multigram scale. In this paper we report that the rhodium(II) carboxylate-catalyzed reaction between vinyldiazomethanes and pyrroles can be used to achieve a general asymmetric synthesis of tropanes as illustrated in eq 1.[6]



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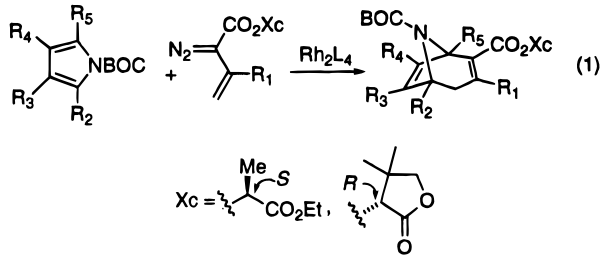

Since our recent publication on the racemic synthesis of tropanes,[7] we have developed two complimentary methods to achieve asymmetric vinylcarbenoid cyclopropanations by using either a chiral rhodium catalyst[8] or a chiral auxiliary on the vinylcarbenoid.[9] Consequently, the vinylcarbenoid chemistry has matured to a stage whereby an asymmetric synthesis of tropanes is feasible.

† State University of New York.
‡ Wake Forest University.
§ Deceased October 19, 1996.
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(1) For a general review, see: (a) Lounasmaa, M.; Tamminen, T. *Alkaloids* **1993**, *44*, 1. (b) Lounasmaa, M. *Alkaloids* **1988**, *33*, 1.

(2) (a) Davies, H. M. L.; Saikali, E.; Huby, N. J. S.; Gilliatt, V. J.; Matasi, J. J.; Sexton, T.; Childers, S. R. *J. Med. Chem.* **1994**, *37*, 1262. (b) Davies, H. M. L.; Kuhn, L. A.; Thornley, C.; Matasi, J. J.; Sexton, T.; Childers, S. R. *J. Med. Chem.* **1996**, *39*, 2554. (c) Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1992**, *35*, 969. (d) Carroll, F. I.; Kotian, P.; Dehghani, A.; Gray, J. L.; Kuzemko, M. A.; Parham, K. A.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1995**, *38*, 379. (e) Kozikowski, A. P.; Roberti, M.; Johnson, K. M.; Bergmann, J. S.; Ball, R. G. *Biorg. Med. Chem. Lett.* **1993**, *3*, 1327. (f) Kozikowski, A. P.; Roberti, M.; Xiang, L.; Bergmann, J. S.; Callahan, P. M.; Cunningham, K. A.; Johnson, K. M. *J. Med. Chem.* **1992**, *35*, 4764. (g) Kelkar, S. V.; Izenwasser, S.; Katz, J. L.; Klein, C. L.; Zhu, N.; Trudell, M. L. *J. Med. Chem.* **1994**, *37*, 3875. (h) Meltzer, P. C.; Liang, A. Y.; Brownell, A.-L.; Elmaleh, D. R.; Madras, B. K. *J. Med. Chem.* **1993**, *36*, 855.

(3) (a) Willstatter, R. *Ber.* **1896**, *29*, 936. (b) Willstatter, R. *Justus Liebigs Ann. Chem.* **1903**, *326*, 23. (c) Robinson, R. *J. Chem. Soc.* **1917**, *111*, 762. (d) Hayakawa, Y.; Baba, Y.; Makino, S.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1786. (e) Tufariello, J. J.; Mullen, G. B.; Tegeler, J. J.; Trybulski, E. J.; Wong, S. C.; Asrof Ali, S. *J. Am. Chem. Soc.* **1979**, *101*, 2435. (f) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Org. Chem.* **1985**, *50*, 1818. (g) Petersen, J. S.; Toteberg-Kaulen, S.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 2948. (h) Rumbo, A.; Mourino, A.; Castedo, L.; Mascarenas, J. L. *J. Org. Chem.* **1996**, *61*, 6114. (i) Dennis, N.; Katritzky, A. R.; Takeuchi, Y. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 1. (j) Rumbo, A.; Mourino, A.; Castedo, L.; Mascarenas, J. L. *J. Org. Chem.* **1996**, *61*, 6114.

(4) (a) Hernandez, A. S.; Thaler, A.; Castells, J.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 314. (b) Majewski, M.; Lazny, R. *J. Org. Chem.* **1995**, *60*, 5825. (c) Rigby, J. H.; Pigge, F. C. *J. Org. Chem.* **1995**, *60*, 7392.

(5) Campbell, H. F.; Edwards, O. E.; Kolt, R. *Can. J. Chem.* **1977**, *55*, 1372.

(6) For preliminary accounts of portions of this work, see: (a) Davies, H. M. L.; Huby, N. J. S. *Tetrahedron Lett.* **1992**, *33*, 6935. (b) Davies, H. M. L.; Matasi, J. J.; Thornley, C. *Tetrahedron Lett.* **1995**, *36*, 7205.

(7) Davies, H. M. L.; Saikali, E.; Young, W. B. *J. Org. Chem.* **1991**, *56*, 5696.

(8) (a) Davies, H. M. L.; Hutcheson, D. K. *Tetrahedron Lett.* **1993**, *34*, 7243. (b) Davies, H. M. L.; Peng, Z.; Houser, J. H. *Tetrahedron Lett.* **1994**, *35*, 8939. (c) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.

(9) (a) Davies, H. M. L.; Huby, N. J. S.; Cantrell, W. R., Jr.; Olive, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 9468. (b) Davies, H. M. L.; Ahmed, G.; Churchill, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10774.

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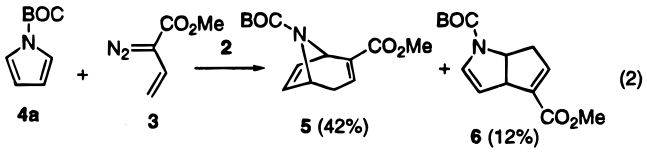
The realization of such an asymmetric approach to tropanes is the focus of this paper, which also emphasizes the range of pyrroles that may be used and the scale-up potential of this chemistry.

Results

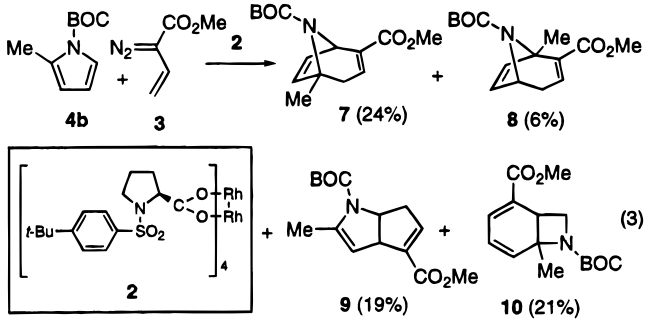
Due to the obvious advantages that would be associated with an asymmetric approach to tropanes using chiral catalysis, a study was undertaken to explore if the rhodium(II) prolinate catalyst **2**[8] would be effective for this chemistry. Earlier studies have shown that a methyl ester-substituted vinyldiazomethane resulted in the highest levels of enantioselectivity;[8a,c] therefore, the vinyldiazomethane **3** was used as the test substrate. All of the test reactions were carried out using hydrocarbon solvents because the use of a nonpolar solvent both enhances the enantioselectivity[8a,c] and limits side reactions occurring through initial attack of the pyrrole at the vinyl terminus of the vinylcarbenoid.[7]

In contrast to the previous results with achiral catalysts,[7] rhodium(II) prolinate (**2**)-catalyzed decomposition of the vinyldiazomethane **3** in the presence of *N*-(BOC)-pyrrole (**4a**) failed to form the tropane product cleanly (eq 2). In addition to the desired tropane **5** (42% yield),



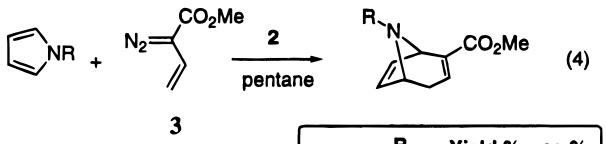
(2)

the isomeric azabicyclo[3.3.0]octane **6** (12% yield) was formed.[6b] Furthermore, the enantioselectivity for the formation of **5** was rather moderate (51% ee), particularly in comparison to the values that have been obtained for the asymmetric cyclopropanation of styrene.[8a,c] Side reactions became even more prevalent when 2-methyl-*N*-BOC-pyrrole (**4b**) was used as substrate (eq 3). Rhodium(II) prolinate (**2**)-catalyzed decomposition of **3** in the presence of **4b** resulted in the formation of two isomeric tropanes, **7** (24% yield) and **8** (6% yield), as well as two other products. The structure of these isomeric products were shown to be the bicyclo[3.3.0]octane **9** (19% yield)[6b] and the bicyclo[4.2.0]octane **10** (21% yield).[6b,10]



(3)

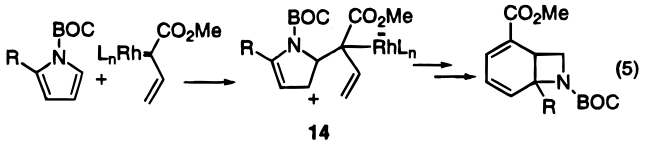
A series of experiments was then directed to determine if the *N*-BOC protecting group on the pyrrole was the most appropriate for this chemistry (eq 4). Although some changes in the enantioselectivity were observed on modifying the protecting group on the pyrrole from *N*-BOC (**5**, 51% ee) to *N*-COOMe (**11**, 42% ee), *N*-acetyl (**12**, 17% ee) or *N*-methanesulfonyl (**13**, 29% ee), no overall improvement in enantioselectivity or yield was observed.



(4)

	R	Yield %	ee %
5	CO_2tBu	42	51
11	CO_2Me	44	42
12	COMe	46	17
13	SO_2Me	34	29

The formation of bicyclo[3.3.0]octane and bicyclo[4.2.0]-octane side products places a serious limitation on the chiral catalyst approach for the asymmetric synthesis of tropanes. Bicyclo[4.2.0]octane formation has been observed in intramolecular reactions between vinylcarbenoids and pyrroles,[10] and it was postulated that they form *via* zwitterionic intermediates arising from electrophilic attack by the carbenoid at the α-position [C(2)] of the pyrrole ring (eq 5). The initial zwitterionic intermediate **14** first undergoes a ring opening to generate a trienimine species, which undergoes successive 8π and 6π electrocyclic reactions to eventually form the bicyclo-[4.2.0]octane nucleus.[10] The formation of bicyclo[3.3.0]-octanes could also be envisioned to occur via zwitterionic intermediates, but the regiochemistry observed in the formation of **9** would require electrophilic attack of the carbenoid at the β-position [C(3)] of the pyrrole ring to form **15** followed by ring closure at C(2) (eq 6). Presumably, the occurence of products derived from zwitterionic intermediates would be enhanced by using electron-deficient catalysts such as the prolinate catalyst **2**.



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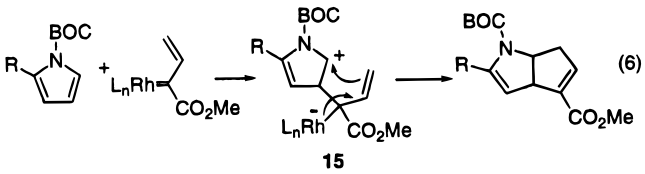


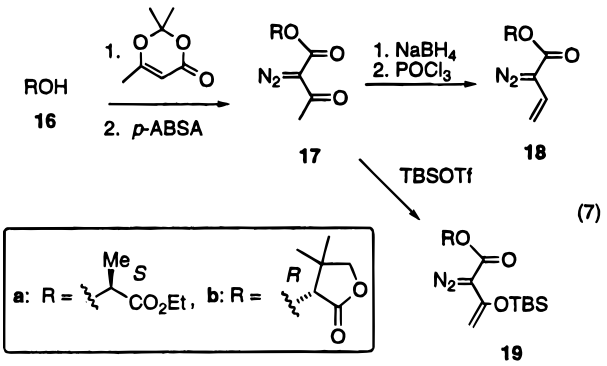
(6)

Due to the mixed results that were obtained using the prolinate catalyst (**2**), attention was then turned to the complimentary method that we have developed for asymmetric vinylcarbenoid transformations using α-hydroxy esters as chiral auxiliaries on the vinylcarbenoid.[9] The cost-effective (*S*)-lactate and (*R*)-pantolactone chiral auxiliaries can offer subtle benefits in addition to serving as the source of chiral induction. During the decomposition of vinyldiazomethanes containing these auxiliaries, the ester carbonyl of the auxiliary is considered to interact with the vinylcarbenoid moiety to form a rigid intermediate, which leads to the possibility of not only high asymmetric induction, but also more selective carbenoid reactivity.[6b]

Vinyldiazomethanes containing the appropriate chiral auxiliaries were prepared by a slight modification of the established procedure (eq 7).[9b] As reasonably large scale

(10) Davies, H. M. L.; Matasi, J. J.; Ahmed, G. *J. Org. Chem.* **1996**, *61*, 2305.

reactions were envisioned, diketene−acetone adduct (2,2,6-trimethyl-4*H*-1,3-dioxin-4-one) was used as the starting material instead of diketene. Reaction of this reagent with ethyl (*S*)-lactate (**16a**) followed by *p*-acetamidobenzenesulfonyl azide[11] (*p*-ABSA), a shock insensitive diazo transfer agent, resulted in the formation of up to 133 g (76% overall yield) of diazocetoacetate **17a**. Conversion of **17a** to the vinyldiazomethane **18a** was readily achieved on a 23 g (100 mmol) scale in 70% yield by successive treatment with sodium borohydride and



phosphorus oxychloride. Silylation of **17a** resulted in the formation of the siloxy-substituted vinyldiazomethane **19a** in essentially quantitative yield. The vinyldiazomethanes **18b** and **19b** containing the (*R*)-pantolactone auxiliary were prepared on a somewhat smaller scale starting from the alcohol **16b** using diketene, and lithium tri-(*tert*-butoxy)aluminium hydride was used instead of sodium borohydride for the initial reduction of **17b**.

Slow addition of the vinyldiazomethane **18a** to a stirred solution of rhodium(II) octanoate and *N*-(BOC)pyrrole (**4a**) in refluxing hexanes resulted in the formation of the tropane **20a** in 82% yield (eq 8, Table 1).[6a] Even though rhodium(II)-catalyzed decomposition of vinyldiazomethanes can occur at temperatures as low as −78 °C, high temperatures and slow addition of the vinyldiazomethane is required in this case in order to avoid biscyclopropanation of the pyrrole.[7] In spite of the rather vigorous reaction conditions, the tropane is formed with a good level of asymmetric induction (66% de) and has been scaled up to produce 37 g (75% yield) of **20a** per reaction. As has been shown previously in other systems,[9] the reaction of **18a** with **4a** is not susceptible to improved stereoselectivity by double stereodifferentiation using either the (*S*)-prolinate catalyst **2** (69% de) or its enantiomer (63% de). The reaction is applicable to a series of 2-substituted pyrroles as shown in Table 1, leading to the formation of tropanes **20b**−**e** in 53−70% de. Unlike the results seen with the prolinate catalysts (eq 2 and 3), no [3.3.0]- or [4.2.0]-bicyclic products are formed in these reactions. Furthermore, the tropane regioselectivity is greater than 10:1 favoring products derived from initial cyclopropanation at the unsubstituted double bond of the pyrrole. Some complications were observed in the reactions of **18a** with 2,5-dimethyl-*N*-(BOC)pyrrole (**4f**) and 3-methyl-*N*-(BOC)pyrrole (**4g**). Unlike the reaction of **18a** with 2-substituted pyrroles, the reaction with **4f** resulted in the formation of both the tropane **20f** and an unstable [3.3.0]bicyclic product analogous to **9** in approximately a 1:1 mixture. Furthermore, the asymmetric induction for the formation of **20f**

(11) Davies, H. M. L.; Cantrell, W. R., Jr.; Romines, K. R.; Baum, J. S. *Org. Synth.* **1991**, *70*, 93.

Table 1. Rhodium(II) Octanoate-Catalyzed Decomposition of 18a or 19a in the Presence of Pyrroles According to Eq 8

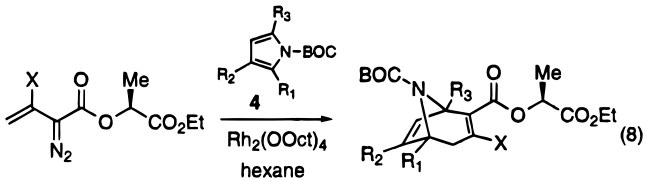
pyrrole	R_1	R_2	R_3	X	product	yield, %	de, %
4a	H	H	H	H	**20a**	82	66
4b	Me	H	H	H	**20b**	54	59
4c	CH_2OTBS	H	H	H	**20c**	62	70
4d	Ph	H	H	H	**20d**	64	53
4e	Ac	H	H	H	**20e**	30	67
4f	Me	H	Me	H	**20f**	33	25
4g	H	Me	H	H	**20g**	19	52
4h	$-(CH_2)_4-$		H	H	**20h**	48	55
4a	H	H	H	OTBS	**21a**	64	66
4b	Me	H	H	OTBS	**21b**	55	58
4d	Ph	H	H	OTBS	**21d**	74	52
4e	Ac	H	H	OTBS	**21e**	58	79
4f	Me	H	Me	OTBS	**21f**	30	52

Table 2. Rhodium(II) Octanoate-Catalyzed Decomposition of 18b or 19b in the Presence of Pyrroles According to Eq 9

pyrrole	R_1	R_2	R_3	X	product	yield, %	de, %
4a	H	H	H	H	**22a**	64	69
4a	H	H	H	OTBS	**23a**	66	68
4d	Ph	H	H	OTBS	**23d**	56	52
4e	Ac	H	H	OTBS	**23e**	69	78
4h	$-(CH_2)_4-$	H		OTBS	**23h**	31	37

was significantly lower (25% de) than the values obtained in earlier systems. In the case of the 3-substituted pyrrole **4g**, the vinylcarbenoid was inefficiently captured (19% yield), but the diastereoselectivity for the formation of **20g** was reasonable (52% de). The reaction could also be extended to the more elaborate pyrrole **4h**, from which the desired tricyclic tropane **20h** was obtained in 48% yield and 55% de.

These reactions were subsequently extended to the 2-(siloxyvinyl)diazomethane **19a** (eq 8, Table 1). Once



18a: X = H
19a: X = OTBS

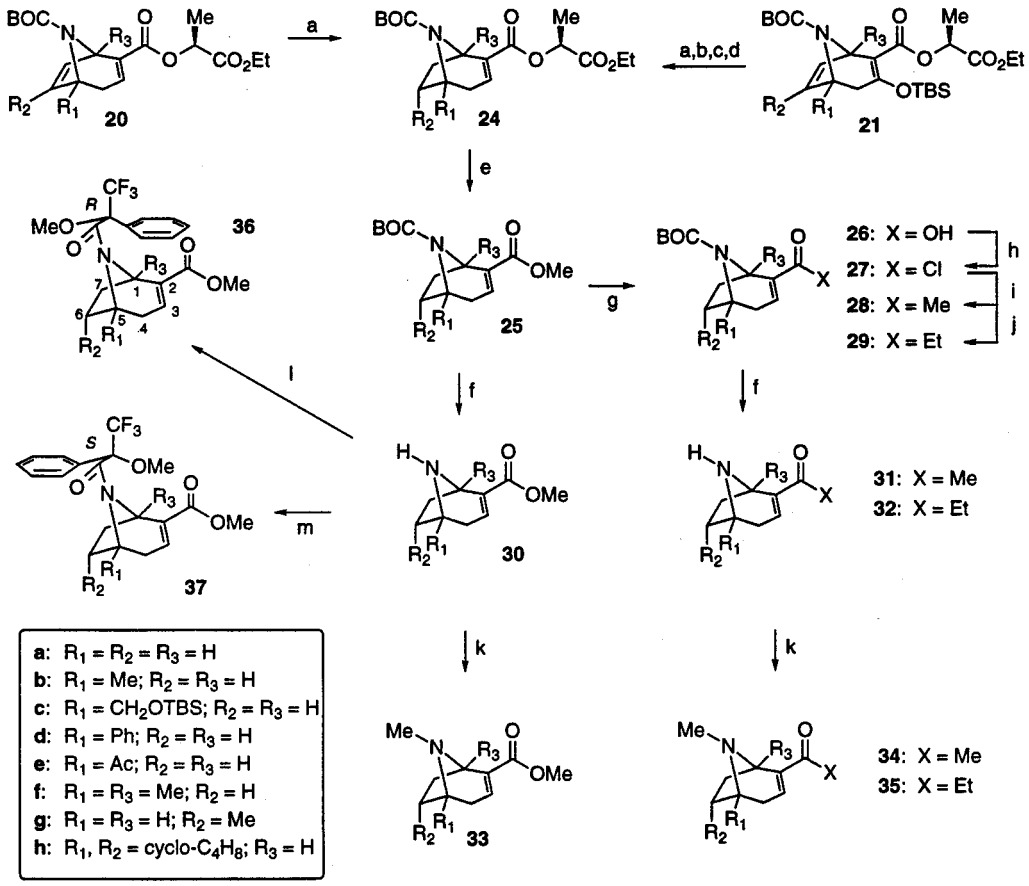
20: X = H
21: X = OTBS

again, reasonable yields and diastereoselectivities of the tropanes **21** were seen with pyrrole and 2-substituted pyrrole derivatives. The highest diastereoselectivity was obtained for the reaction with 2-acetylpyrrole (**4e**). In this case, moderate double stereodifferentiation was observed where the diastereoselectivity for **21e** improved from 79% to 88% de on changing the catalyst from rhodium(II) octanoate to the (*S*)-prolinate derivative **2**.

The enantiomeric series of tropanes were obtained starting from vinyldiazomethanes **18b** and **19b** containing (*R*)-pantolactone as the chiral auxiliary (eq 9, Table 2). The diastereoselectivity of the tropanes **22** and **23** obtained from these diazomethanes and various pyrroles was roughly parallel to the results observed with the (*S*)-lactate auxiliary and ranged from 37−78% de.

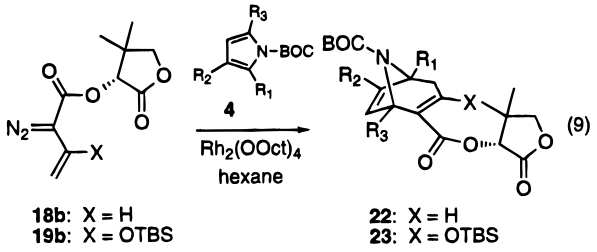
The absolute stereochemistry of the tropanes was determined by conversion of selected members to known compounds and/or by comparison of chemical shift differences of Mosher amide derivatives for a series of compounds. The synthetic interconversions are summarized in Scheme 1. Verification that the same sense of asymmetric induction was obtained from both the

Scheme 1



(a) H_2, $(PPh_3)RhCl$ (b) TBAF (c) NaHMDS, $PhNTf_2$ (d) $PdCl_2$, HCO_2H, Bu_3N (e) NaOMe (f) TFA (g) $LiOH{\bullet}H_2O$ (h) $SOCl_2$ (i) MeMgBr, $CuBr{\bullet}SMe_2$ (j) Et_2Zn, $Pd_2(dba)_3$ (k) HCHO, $Na(CN)BH_3$ (l): (*S*)-MTPA-Cl, *i*-Pr_2EtN (m) (*R*)-MTPA-Cl, *i*-Pr_2EtN

siloxy- and unsubstituted vinyldiazomethanes was confirmed by conversion of both **20a** and **21a** to tropane **24a**.



18b: X = H
19b: X = OTBS

22: X = H
23: X = OTBS

High field ^1H NMR analysis of both samples of **24a** at 95 °C (to avoid broadening of signals due to hindered amide rotation) showed that in both cases the same diastereomer predominated. The absolute stereochemistry of the major diastereomer of **24a** was determined by conversion to (−)-anhydroecgonine methyl ester (**33a**) by removal of both the chiral auxiliary and BOC group followed by reductive methylation. In a similar series of reactions on **22a**, it was possible to show that (*R*)-pantolactone auxiliary resulted in tropane formation with opposite asymmetric induction to that obtained with the (*S*)-lactate auxiliary.[6a]

The absolute stereochemistry determined for **20a** is opposite to that expected from the model we have developed for asymmetric induction in related reactions (See Discussion). Consequently, the determination of the absolute stereochemistry for a series of compounds in addition to **20a** was deemed to be necessary. This was achieved by the procedure developed by Hoye *et al.*[12] Tropanes **20** were converted to the secondary amines **30** and then to their (*R*)- and (*S*)-Mosher [methoxy(trifluoromethyl)phenylacetyl] amides (**36**, **37**) by treatment of the corresponding amine with the appropriate acid chloride in the presence of diisopropylethylamine (Scheme 1).[13] As is observed for other secondary amines,[12] each Mosher amide adopts a conformation where the trifluoromethyl group is syn-periplanar to the carbonyl group. Consequently, specific ^1H NMR resonances for the tropane ring are predictably shifted upfield by the presence of the phenyl group on the Mosher amide.[12a,14] In the case of enantiomerically pure demethylated (−)-anhydroecgonine methyl ester (**30a**), each Mosher amide exists as a mixture of two rotamers where the major rotamer has the Mosher amide stereogenic center *syn* to the C(2)-carbomethoxy substituent.[15] The major rotamer for the *S*-Mosher amide **37a** is characterized by a strongly

(12) (a) Hoye, T. R.; Renner, M. K. *J. Org. Chem.* **1996**, *61*, 2056 and references therein. (b) Hoye, T. R.; Renner, M. K. *J. Org. Chem.*, in press. (c) Rauk, A.; Tavares, D. F.; Khan, M. A.; Borkent, A. J.; Olson, J. F. *Can. J. Chem.* **1983**, *61*, 2572.

(13) Due to the differences in the priority assigned to a dialkylamino group versus a chloro group, the *R*-acid chloride produces the *S*-Mosher amide.

(14) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(15) The opposite rotamer is observed exclusively for the Mosher amides of norcocaine described in ref 12b, presumably due to the presence of β-substituents at C2 and C3.

Table 3. ^{1}H NMR Chemical Shift Differences ($\delta S - \delta R$) of Mosher Amides of Selected Tropanes (*syn* rotamer)

tropane	R_1	R_2	R_3	H(1)	H(3)	H(4β)	H(4α)	H(5)	H(7β)	R(1)	R(2)
30a	H	H	H	−0.11	+0.35	−0.07	+0.12	+0.17	-0.93	−	−
30b	Me	H	H	−0.15	+0.28	−0.11	+0.09	−	-0.97	+0.07	−
30d	Ph	H	H	−0.28	+0.34	−0.03	+0.05	−	-0.82	−	−
30e	Ac	H	H	−0.42	+0.41	0.00	+0.06	−	-0.72	+0.02	−
30g	H	Me	H	−0.11	+0.34	−0.07	+0.14	+0.15	-0.92	−	−0.03
30h	-$(CH_2)_4$-		H	−0.32	+0.27	−0.33	+0.08	−	-0.91	−	−

Table 4. ^{1}H NMR Chemical Shift Differences ($\delta S - \delta R$) of Mosher Amides of Selected Tropanes (*anti* rotamer)

tropane	R_1	R_2	R_3	H(1)	H(3)	H(4β)	H(4α)	H(5)	R(2)
30a	H	H	H	−0.12	−0.28	−1.87	−0.55	+0.47	−
30g	H	Me	H	−0.11	−0.29	−1.88	−	+0.44	+0.20

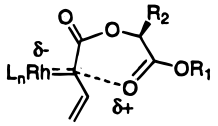
shielded 7β proton resonance which is 0.93 ppm upfield (500 MHz, $CDCl_3$) from the corresponding resonance for the *R*-amide **36a**. The minor rotamer of **37a**, where the phenyl group is shielding the 4-position, also shows distinctly shifted proton resonances. In this compound, the 4β proton resonance appears at 0.89 ppm, *1.87 ppm* upfield from the corresponding resonance of the *R*-derivative. Taken together, these data are consistent with **30a** having the established (1*R*,5*S*)-absolute stereochemistry.[5]

Using this method, the absolute stereochemistry of tropanes **30b**,**d**,**e**,**g**,**h**, all generated using the lactate chiral auxiliary, was evaluated. While the analysis was slightly more complicated due to the fact that these tropanes were enriched rather than enantiomerically pure, this was mitigated by the fact that in most cases only one amide rotamer was observed for each enantiomer.[16] In all cases, the absolute stereochemistry was assigned to be 1*R*. Selected ^{1}H NMR data for all of the Mosher amides prepared are summarized in Tables 3 and 4.

The impetus behind this research was to develop a practical asymmetric synthesis of the tropanes **30**−**35**, as these are the key starting materials for our collaborative projects directed toward the development of medications for the treatment of cocaine addiction.[17] Normethyl anhydroecgonine methyl ester (**30a**) was routinely obtained in 20 g quantities in 60−70% ee from **18a** and was resolved into enantiomerically pure form by recrystallization (three times) of its diastereomeric di-*p*-toluoyl-D-tartrate salt (**38a**). Enriched BOC-protected anhydroecgonine methyl ester (**25a**) was converted to either **31a** or **32a** by initial hydrolysis to the acid (**26a**) followed by conversion to the acid chloride (**27a**). Alkylation was achieved either by the corresponding organocuprate or dialkyl zinc reagent, which was subsequently followed by removal of the BOC group. The conversion of **25a** to the deprotected enriched tropane **32a** has been carried out on up to a 10 g scale in 45−55% overall yields. The resolution of **31a** and **32a** was also achieved via recrystallization of their di-*p*-toluoyl tartrate salts; in the case of **32a**, enantiomerically pure tropane has been obtained on a gram scale in up to 48% overall yield from the pure BOC-protected enriched intermediate **29a**. Enantiomerically pure tropanes **33**−**35** were easily obtained via reductive methylation of **30**−**32**.

Discussion

The reaction of vinyldiazomethanes with suitably protected pyrroles has proven to be a valuable and efficient route into the tropane ring system. During the course of the study, this reaction has been optimized and improved to the point where multigram quantities of enantiomerically enriched tropanes with a variety of substitution patterns can be synthesized with relative ease. This has been achieved even though the electron-rich nature of the pyrrole system shows a tendency toward formation of stabilized zwitterionic intermediates leading to the formation of [3.3.0]- and [4.2.0]-bicyclic side products. The formation of these products is further amplified when the chemistry is carried out with the chiral prolinate catalyst **2**, which is presumably more electrophilic than the rhodium octanoate catalyst. This problem was circumvented to a great extent by employing a chiral α-hydroxy ester functionality on the vinyl carbenoid system. These auxiliaries not only result in enhanced formation of tropanes, but also enable the transformation to be carried out with a reasonable level of asymmetric induction. Several of the enantioenriched tropanes were conveniently resolved to the pure enantiomers.



41

The use of α-hydroxyesters as chiral auxiliaries for carbenoid reactions is becoming well established.[9] The high asymmetric induction that occurs using these auxiliaries is considered to be due to an interaction between the ester carbonyl of the auxiliary and the carbenoid, resulting in a rigid orientation (**41**) during the cyclopropanation step. However, the asymmetric induction observed in these reactions with pyrroles is opposite to what has been found in related systems. For example, the reaction of vinyldiazomethane **18a** with furan results in the formation of a (1*S*)-oxabicyclo[3.2.1]octane product in 80% de,[9b] but the reaction of **18a** with pyrroles results in the predominant formation of (1*R*)-tropanes. In the standard model,[9] as illustrated in Figure 1 for the lactate auxiliary, the favored interaction of the auxiliary with the carbenoid has the methyl group of the stereogenic center pointing away from the bulk of the catalyst such that only one face of the carbenoid is open. Even with

(16) The major rotamer observed with one Mosher amide derived from one enantiomer of tropane is *enantiomeric* with the major rotamer derived from the opposite enantiomer of tropane with the opposite Mosher amide. Since these two compounds have identical NMR spectra, mixtures of Mosher amides can striaghtforwardly be assigned.

(17) (a) Porrino, L. J.; Migliarese, K.; Davies, H. M. L.; Saikali, E.; Childers, S. R. *Life Sci.* **1994**, *54*, 511−517. (b) Hemby, S. E.; Co, C.; Reboussin, D.; Davies, H. M. L.; Dworkin, S. I.; Smith, J. E. *J. Pharmacol. Exp. Ther.* **1995**, *272*, 1176−1186. (c) Porrino, L. J.; Davies, H. M. L.; Childers, S. R. *J. Pharmacol. Exp. Ther.* **1995**, *272*, 901.

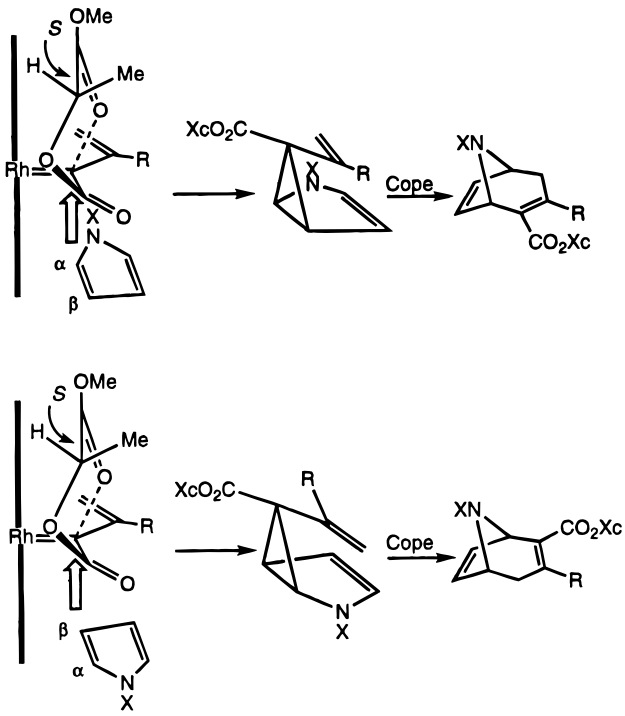
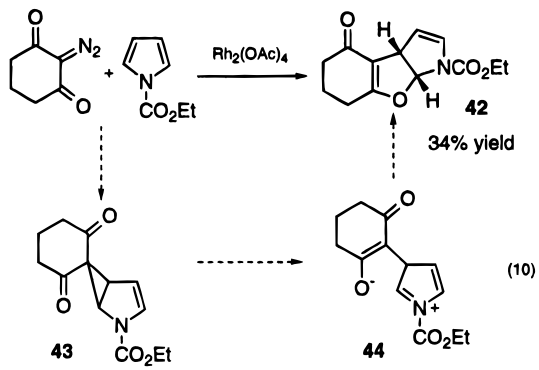


Figure 1.

one face of the carbenoid fully blocked, it is still possible for the reaction with pyrrole to result in the formation of either enantiomer of the tropane depending on how the pyrrole approaches the open face of the carbenoid. As shown in Figure 1, two enantiomeric tropanes could be formed depending on whether the nonsynchronous cyclopropanation occurs with greater initial bonding to the α or the *β* position of the pyrrole. Normally, electrophilic attack at the α-position of the pyrrole is electronically favored, but it has been previously established that bulky substituents on the pyrrole redirect electrophilic attack to the *β*-position.[18] The observed asymmetric induction would require the nonsynchronous cyclopropanation to occur with greater initial bond formation at the *β*-position of **4**, which is reasonable considering the presence of the bulky BOC-substituent present on the nitrogen and the large size of the electrophilic carbenoid species. Furthermore, electron-withdrawing substituents at the 2-position of pyrroles are known to direct electrophilic attack to the *β*-position on the opposite side of the ring.[18] It is therefore not surprising that the highest diastereoselectivities are obtained with the 2-acetylpyrrole **4e**. Certainly, the formation of [3.3.0]-bicyclic products **6** and **9** in the reactions using the prolinate catalyst **2** demonstrate that it is feasible for carbenoids to react at the *β*-position of this pyrrole system.

The observation that carbenoids are capable of electrophilic attack at the 3-position of *N*-BOC-pyrrole may shed light on other carbenoid reactions that have stood out as rather unusual transformations. For example, Pirrung and co-workers have discovered a very useful 3 + 2 annulation between diazodimedone and *N*-(ethoxycarbonyl)pyrrole leading to the tricyclic product **42** (eq 10).[19] The regiochemistry of the reactions is not consistent with the formation of zwitterionic intermediates through attack at the α-position of the pyrrole. Consequently, Pirrung proposed that the reactions occurred through initial cyclopropanation followed by ring-opening of the pyrrolocyclopropane **43** to a zwitterionic intermediate **44**. However, the regiochemical issue is still problematical, and furthermore, the carbenoid derived from diazodimedone is highly electrophilic such that the reaction with pyrrole would be expected to directly form zwitterionic intermediates. A very plausible explanation for this apparently unusual regiochemistry is that the reaction is simply an example of a bulky rhodium−carbenoid complex reacting at the *β*-position of the pyrrole, leading directly to the zwitterionic intermediate **44**.



In summary, the reaction between rhodium-stabilized vinylcarbenoids and pyrroles leads to the general synthesis of tropanes. Of the two complimentary methods available for asymmetric vinylcarbenoid transformations, the most effective for pyrroles is the use of α-hydroxy esters as chiral auxiliaries on the carbenoid.

Experimental Section

^{1}H NMR spectra were run at either 200, 300, 400, or 500 MHz, and ^{13}C NMR at either 50, 75, or 125 MHz in $CDCl_3$ unless otherwise noted. Mass spectral determinations were carried out at 70 eV. Hexanes, THF, and Et_2O were dried over and distilled from sodium metal with benzophenone as the indicator. Acetonitrile and methylene chloride were dried over and distilled from CaH_2. Pentane was dried over activated molecular sieves (4 Å) for 24 h prior to use. Column chromatography was carried out on Merck silica gel 60 (230−400 mesh). Commercially available reagents were used without additional purification unless noted. Melting points are uncorrected. *p*-Acetamidobenzenesulfonyl azide (*p*-ABSA),[11] the chiral rhodium prolinate catalyst **2**,[8c] vinyl diazomethanes **3**,[7] **19a**,[9b] **19b**,[9b] *N*-(methoxycarbonyl)pyrrole,[20] *N*-acetylpyrrole,[21] *N*-(methanesulfonyl)pyrrole,[22] 2-phenylpyrrole,[23] 2,5-dimethyl-1-[(1,1-dimethylethoxy)carbonyl]pyrrole (**4f**),[24] and 4,5,6,7-tetrahydroindole (**4h**)[23] were prepared by literature procedures. 2-Methyl and 3-methylpyrrole were prepared from the corresponding carboxaldehydes via Wolff−Kishner reduction.[18,25] Unless otherwise stated, enantiomeric excesses of the [3.2.1] ring systems were determined by gas chromatography on a permethylated *β*-cyclodextrin (*β*-PH) column obtained from Astec Separations connected to a Hewlett-Packard 5890 Series II Plus gas chromatograph.

(18) Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. *J. Org. Chem.* **1990**, *55*, 6317 and references therein.

(19) Pirrung, M. C.; Zhang, J.; Lackey, K.; Sternbach, D. D.; Brown, F. *J. Org. Chem.* **1995**, *60*, 2112.

(20) Acheson, R. M.; Vernon, J. M. *J. Chem. Soc.* **1961**, 457.

(21) Reddy, G. S. *Chem. Ind.* **1965**, 1426.

(22) Prinzbach, H.; Kaupp, G.; Fuchs, R.; Joyeux, M.; Kitzing, R.; Markert, J. *Chem Ber.* **1973**, *106*, 3824.

(23) Mikhaleva, A. I.; Trofimov, B. A.; Vasil'ev, A. N.; Komarova, G. A.; Skorobogatova, V. I. *Khim. Geterotsikl. Soedin.* **1983**, 920.

(24) Chen, W.; Cava, W. P. *Tetrahedron Lett.* **1987**, *28*, 6025.

(25) Cornforth, J. W.; Firth, M. E. *J. Chem. Soc.* **1958**, 1091.

Synthesis of *N*-BOC-Protected Pyrroles (4). Typical Procedure.[2a] A solution of 2-methylpyrrole (14.0 g, 173 mmol) and 4-(dimethylamino)pyridine (DMAP, 1.59 g, 13.0 mmol) in dry acetonitrile (25 mL) was prepared, and di-*tert*-butyl dicarbonate (46.8 g, 204 mmol) was added. The reaction was stirred at rt for 4 days, and the solvent was removed under vacuum. The crude product was purified by silica gel chromatography (petroleum ether mobile phase) to give **1-[(1,1-Dimethylethoxy)carbonyl]-2-methylpyrrole (4b)** as an oil. Yield: 22.4 g (124 mmol, 71%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.18 (br t, J = 2.1 Hz, 1H), 6.05 (dd, J = 3.4, 2.1 Hz, 1H), 5.92 (br s, 1H), 2.40 (s, 3H), 1.58 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.7, 131.5, 120.5, 111.8, 109.9, 83.1, 28.0, 15.4; IR (neat) 3110, 2981, 2929, 2867, 1740, 1584, 1497, 1403, 1372 cm^{-1}; HRMS calcd for $C_{10}H_{15}NO_2$ 181.1103; found 181.1104.

Pyrroles **4b**, **4d**, **4e**, **4g**, and **4h** were prepared using a similar procedure; the chromatography solvent system, amount of material, and yield of these compounds are given in parentheses.

2-[(*tert*-Butyldimethylsiloxy)methyl]-1-[(1,1-dimethylethoxy)carbonyl]pyrrole (4c). Imidazole (3.16 g, 46.4 mmol) was added to a solution of 2-(hydroxymethyl)-*N*-BOC-pyrrole[10] (4.57 g, 23.2 mmol) and *tert*-butyldimethylsilyl chloride (5.25 g, 34.8 mmol) in anhydrous DMF (30 mL). The mixture was stirred for 20 h and then diluted with Et_2O and washed with water and brine. The ether solution was dried ($MgSO_4$) and evaporated. The crude product was then chromatographed (9:1 petroleum ether/Et_2O) to give the title product as an oil. Yield: 6.52 g (20.9 mmol, 90%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.19 (m, 1H), 6.22 (m, 1H), 6.13 (t, J = 3.3 Hz, 1H), 4.89 (s, 2H), 1.59 (s, 9H), 0.93 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 135.5, 121.0, 111.1, 110.3, 83.5, 60.1, 27.8, 25.8, 18.2, −5.5; IR (neat) 3157, 3116, 2960, 2929, 2883, 2862, 1745, 1502, 1476, 1419, 1372, 1336 cm^{-1}. Anal. Calcd for $C_{16}H_{29}NO_3Si$: C, 61.69; H, 9.38; N, 4.50. Found: C, 61.57; H, 9.37; N, 4.52.

1-[(1,1-Dimethylethoxy)carbonyl]-2-phenylpyrrole (4d) (petroleum ether, 2.43 g, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.38 (m, 5H), 7.32 (dd, J = 3.4, 1.8 Hz, 1H), 6.24 (dd, J = 3.4, 3.1 Hz, 1H), 6.20 (dd, J = 3.1, 1.8 Hz, 1H), 1.36 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 135.7, 135.1, 129.8, 128.1, 127.7, 123.1, 114.9, 111.0, 83.9, 27.8; IR (neat) 3069, 3028, 2981, 2940, 1740, 1610, 1512, 1471, 1393, 1347 cm^{-1}. HRMS calcd for $C_{15}H_{17}NO_2$ 243.1259; found 243.1253.

2-Acetyl-1-[(1,1-dimethylethoxy)carbonyl]pyrrole (4e) (hexane/Et_2O, 9:1−4:1, 19.2 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 1H), 6.84 (m, 1H), 6.16 (t, J = 3.4 Hz, 1H), 2.44 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.8, 149.2, 134.4, 128.0, 121.2, 110.0, 84.8, 27.7, 27.3; IR (neat) 3131, 2981, 2934, 1750, 1678, 1543, 1481, 1450, 1419, 1310, 1150 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.24; H, 7.24; N, 6.72.

1-[(1,1-Dimethylethoxy)carbonyl]-3-methylpyrrole (4g) (petroleum ether, 2.74 g, 49%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.12 (t, J = 2.7 Hz, 1H), 6.95 (m, 1H), 6.03 (dd, J = 3.1, 1.8 Hz, 1H), 2.04 (s, 3H), 1.56 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 122.5, 120.0, 117.3, 114.1, 83.0, 27.7, 11.5; IR (neat) 3152, 2986, 2924, 2878, 1740, 1559, 1491, 1393, 1346, 1253 cm^{-1}. HRMS calcd for $C_{10}H_{15}NO_2$ 181.1103; found 181.1101.

1-[(1,1-Dimethylethoxy)carbonyl]-4,5,6,7-tetrahydroindole (4h) (petroleum ether, 7.30 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, J = 3.4 Hz, 1H), 5.95 (d, J = 3.4 Hz, 1H), 2.79 (t, J = 6.4 Hz, 2H), 2.42 (t, J = 6.0 Hz, 2H) 1.74 (m, 2H), 1.68 (m, 2H), 1.55 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.53, 129.33, 121.95, 119.08, 110.84, 82.54, 27.77, 24.52, 23.16, 22.60; IR (neat) 2971, 2933, 2851, 1734, 1368, 1324, 1160, 1128 cm^{-1}; MS *m/e* (relative intensity) 221 (M^+) (8), 166 (4), 165 (38), 148 (4), 121 (19), 120 (18), 93 (63), 57 (100). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.34; H, 8.69; N, 6.10.

Rhodium(II) Carboxylate-Catalyzed Decomposition of Vinyldiazomethanes in the Presence of Pyrroles. Typical Procedure. A solution of vinyldiazomethane (2.4 mmol) in dry hexanes (50 mL) was added dropwise over 1 h to a refluxing solution of pyrrole (12.0 mmol) and rhodium(II) carboxylate (0.01 equiv) in dry hexanes (50 mL) under an atmosphere of argon. After the addition was complete, the mixture was refluxed for 1 h. The solvent was removed under reduced pressure, and the excess pyrrole was removed from the crude reaction mixture either by Kugelrohr distillation or flash chromatography on silica gel using petroleum ether as the eluant. The remaining organics were eluted with either petroleum ether/Et_2O or hexanes/EtOAc as the eluant. For compounds **5**−**13**, **20a**, **21a**, **22a**, and **23a**, the catalyst, chromatography solvent system, isolated quantity of product, yield, and diastereoselectivity/enantioselectivity for each reaction are presented in that order in parentheses. This information, as well as characterization data for the remaining tropanes are provided in the Supporting Information.

Methyl 8-[(1,1-Dimethylethoxy)carbonyl]-8-azabicyclo-[3.2.1]octa-2,6-diene-2-carboxylate (5) and Methyl 1-[(1,1-Dimethylethoxy)carbonyl]-1,3,6,6a-tetrahydrocyclopenta[b]pyrrole-4-carboxylate (6) (**2**, 9:1−4:1 pentane/Et_2O):

5: 0.479 g, 42% yield, 51% ee; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.47 (br s, 1H), 6.38 (br s, 1H), 5.88 (br s, 1H), 4.93 (br s, 1H), 4.55 (br s, 1H), 3.69 (s, 3H), 2.80 (br d, J = 19.4 Hz, 1H), 1.85 (br d, J = 19.8 Hz, 1H), 1.35 (s, 9H); IR (neat) 2985, 1700, 1625, 1435, 1375, 1315, 1230, 1160, 1095, 1070, 1030 cm^{-1}; MS *m/e* 279 (M^+), 207, 167, 149, 113, 112, 83, 71, 70, 69, 57, 43. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.24; H, 7.18; N, 5.23.

6: 0.141 g, 12%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.69 (t, J = 2.2 Hz, 1H), 6.53 (dd, J = 4.2, 1.6 Hz, 0.4H, minor rotamer), 6.41 (dd, J = 4.2, 1.6 Hz, 0.6H, major rotamer), 5.19 (m, 1H), 4.74 (qd, J = 9.3, 2.7 Hz, 1H), 4.24 (br t, J = 9.6 Hz, 1H), 3.72 (s, 3H), 3.02 (dd, J = 20.0, 9.9 Hz, 1H), 2.76 (br d, J =18 Hz, 0.6H, major rotamer), 2.67 (br d, J = 18 Hz, 0.4H, minor rotamer), 1.44 (s, 9H); IR ($CDCl_3$) 2980, 2953, 1691, 1613, 1439, 1409, 1384, 1257, 1132, 1030 cm^{-1} ; MS *m/e* 265 (M^+), 234, 209, 192, 177, 149, 133, 105, 77, 57. HRMS calcd for $C_{14}H_{19}NO_4$ 265.1314; found 265.1315.

Methyl 8-[(1,1-Dimethylethoxy)carbonyl]-5-methyl-8-azabicyclo[3.2.1]octa-2,6-diene-2-carboxylate (7), Methyl 8-[(1,1-Dimethylethoxy)carbonyl]-1-methyl-8-azabicyclo-[3.2.1]octa-2,6-diene-2-carboxylate (8), Methyl 1-[(1,1-Dimethylethoxy)carbonyl]-2-methyl-1,3,6,6a-tetrahydrocyclopenta[b]pyrrole-4-carboxylate (9), and Methyl 7-[(1,1-Dimethylethoxy)carbonyl]-6-methyl-7-azabicyclo[4.2.0]octa-2,4-diene-2-carboxylate (10) (**2**, 4:1 pentane/Et_2O):

7: 0.241 g, 24% yield, 46% ee; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.60 (br t, J = 3.6 Hz, 1H), 6.24 (dd, J = 6.1, 2.7 Hz, 1H), 5.57 (d, J = 6.1 Hz, 1H), 5.00 (br s, 1H), 3.72 (s, 3H), 2.82 (br d, J = 19.8 Hz, 1H), 1.92 (dd, J = 19.8, 3.8 Hz, 1H), 1.65 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.4, 154.8, 137.5, 135.2, 134.0, 79.9, 63.4, 59.8, 51.7, 28.3, 22.7; IR ($CDCl_3$) 3157, 2954, 2904, 1794, 1701, 1628, 1607, 1561, 1476, 1457 cm^{-1}; MS *m/e*: 279 (M^+), 248, 223, 191, 179, 147, 119, 91, 77, 57. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.48; H, 7.58; N, 5.02. Found: C, 64.73; H, 7.63; N, 4.91.

8: 0.060 g, 6% yield, ∼0% ee; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.34 (br s, 1H), 6.18 (d, J = 6.1 Hz, 1H), 5.78 (dd, J = 6.1, 2.6 Hz, 1H), 5.59 (m, 1H), 3.70 (s, 3H), 2.90 (br d, J = 15.3 Hz, 1H), 1.81 (s, 3H), overlapping a doublet of doublet at δ 1.85 (dd, J = 15.3, 3.2 Hz, 1H), 1.42 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.2, 154.3, 144.0, 140.7, 134.9, 124.9, 79.8, 63.9, 59.2, 51.4, 28.2, 26.9, 20.5; IR ($CDCl_3$) 2982, 2953, 1712, 1612, 1475, 1457, 1437, 1412, 1382, 1369 cm^{-1}; MS *m/e*: 279 (M^+), 223, 191, 179, 163, 147, 119, 91, 77, 57.

9: 19%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.68 (m, 1H), 4.90 (dd, J = 2.4, 1.2 Hz, 1H), 4.82 (ddd, J = 9.8, 9.8, 3.0 Hz, 1H), 4.05 (m, 1H), 3.70 (s, 3H), 2.55−2.90 (m, 2H), 2.05 (br s, 3H), 1.37 (s, 9H). Compound **9** could not be isolated in pure form and fully characterized due to its decomposition during chromatography. The structural assignment is based on the similarity of the NMR data of **9** to that of **6**, and the yield was calculated from integration of the ^{1}H NMR spectrum of the crude reaction mixture.

10: 0.211 g, 21%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 6.89 (d, J = 5.4 Hz, 1H), 6.08 (m, 2H), 4.45 (dd, J = 7.9, 6.7 Hz, 1H), 4.12 (dd, J = 7.9, 7.9 Hz, 1H), 3.71 (s, 3H), 3.32 (dd, J = 7.9,

6.7 Hz, 1H), 1.56 (s, 3H), 1.41 (s, 9H); IR ($CDCl_3$) 3154, 3046, 2979, 2954, 2931, 1792, 1587, 1499, 1475, 1458 cm^{-1}. Compound **10** decomposes to give methyl 3-methylbenzoate.

Methyl 8-(Methoxycarbonyl)-8-azabicyclo[3.2.1]octa-2,6-diene-2-carboxylate[7] (11) (**2**, 4:1−1:1 pentane/Et_2O, 0.396 g, 44% yield, 42% ee).

Methyl 8-Acetyl-8-azabicyclo[3.2.1]octa-2,6-diene-2-carboxylate (12) (**2**, 3:1−9:1 EtOAc/hexanes, 0.262 g, 46% yield, 17% ee). ^1H NMR (200 MHz, $CDCl_3$, rotamers) δ 6.54 (m, 1H), 6.45 (dd, J = 6.0, 2.6 Hz, 1H), 5.94 (dd, J = 6.0, 2.6 Hz, 1H), 5.42 (m, 0.25H), 4.97 (t, J = 1.1, 1.5H), 4.58 (m, 0.25H), 3.74 (s, 3H), 2.86 (ddd, J = 20.0, 5.8, 3.1 Hz, 0.75H), 2.68 (ddd, J = 19.5, 5.4, 2.9 Hz, 0.25H), 2.07 (dd, J = 19.7, 4.0 Hz, 0.25H), 2.02 (s, 0.75H), 1.97 (s, 2.25H), 1.92 (dd, J = 20.0, 4.0 Hz, 0.75H). HRMS calcd for $C_{11}H_{13}NO_3$ 207.0895; found 207.0895.

Methyl 8-(Methylsulfonyl)-8-azabicyclo[3.2.1]octa-2,6-diene-2-carboxylate (13) (**2**, 1:1−1:4 pentane/Et_2O, 0.134 g, 34% yield, 29% ee as determined by ^1H NMR using 17 mol % $Pr(hfc)_3$ in $CDCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 6.56 (m, 1H), 6.53 (dd, J = 5.8, 2.1 Hz, 1H), 5.93 (dd, J = 5.8, 2.1 Hz, 1H), 5.11 (d, J = 1.1 Hz, 1H), 4.70 (d, J = 6.0 Hz, 1H), 3.75 (s, 3H), 2.86 (ddd, J = 19.8, 5.8, 2.9 Hz, 1H), 2.67 (s, 3H), 2.07 (dd, J = 19.6, 3.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.4, 138.3, 135.7, 130.0, 127.6, 59.7, 58.9, 52.0, 38.4, 29.0. Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.37; H, 5.39; N, 5.76. Found: C, 49.31; H, 5.43; N, 5.65.

(1*S*)-2-Ethoxy-1-methyl-2-oxoethyl 2-diazo-3-oxobutanoate (17a). A solution of (*S*)-ethyl lactate (100 g, 0.848 mol) and 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (diketene−acetone adduct, 100 mL, 0.766 mol) was prepared in 400 mL toluene. The reaction was heated to reflux for 2 h and then allowed to cool to room temperature. The solvent was evaporated under reduced pressure to give (1*S*)-2-Ethoxy-1-methyl-2-oxoethyl 3-oxobutanoate (150 g) as a dark oil, which was used without further purification for the next step.

A solution of all of the above material in 2 L acetonitrile was prepared, and *p*-acetamidobenzenesulfonyl azide (*p*-ABSA, 194 g, 0.808 mol) was added with mechanical stirring. Triethylamine (116 mL, 832 mmol) was then added, and a cream-colored precipitate formed within 1 min. The reaction was stirred for 12 h at room temperature. The reaction mixture was filtered, and the filter cake washed with Et_2O. The filtrate was evaporated to give a tacky, oily solid which was triturated thoroughly with 1:1 petroleum ether/Et_2O and filtered. The filtrate was evaporated to give a light brown oil, which was then chromatographed on silica gel (4:1 petroleum ether/Et_2O) to give the title compound as a pale yellow oil. Yield: 133 g (0.583 mol, 76% overall). ^1H NMR (200 MHz, $CDCl_3$) δ 5.18 (q, J = 7.1 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 2.45 (s, 3H), 1.52 (d, J = 7.1 Hz, 3H),1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 189.0, 170.0, 160.3, 75.7, 68.9, 65.3, 27.6, 16.4, 14.8, 13.6; IR (neat) 2980, 2135, 1715, 1655, 1360, 1210, 1095 cm^{-1}; $[\alpha]^{25}_D$ = +31.4° ($CDCl_3$, *c* 5.06). Anal. Calcd for $C_9H_{12}N_2O_5$: C, 47.37; H, 5.30; N, 12.28. Found: C, 47.43; H, 5.35; N, 12.18.

(*R*)-Tetrahydro-4,4-dimethyl-2-oxofuranyl 2-Diazo-3-oxobutanoate (17b). To a solution of (*R*)-pantolactone (20.0 g, 0.154 mol) and pyridine (1.5 mL, 18.5 mmol) in dry acetonitrile (150 mL) was added diketene (14.2 g, 0.169 mol), and the mixture was heated to reflux for 2 h. Additional diketene (11.6 g, 0.138 mol) was added, and the heating was continued for an additional 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (400 mL), washed with $CuSO_4$ (aqueous 100 mL), $NaHCO_3$ (saturated aqueous 100 mL), dried (Na_2SO_4), and concentrated to give a brown oil (46.2 g). Distillation (120−130 °C, 0.2 mmHg) gave an impure acetoacetate which was further purified by trituration with 10% Et_2O in pentane to give pure (*R*)-tetrahydro-4,4-dimethyl-2-oxo-3-furanyl 3-oxobutanoate (16.3 g, 75%) as a pale yellow solid (mp = 38−44 °C). ^1H NMR (200 MHz, $CDCl_3$) δ 5.41 (s, 1H), 4.04 (s, 2H), 3.62 (s, 1H), 3.60 (s, 1H), 2.30 (s, 3H), 1.24 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.5, 171.7, 165.6, 75.8, 75.2, 49.2, 40.1, 29.9, 22.4, 19.5; MS *m/e* (relative intensity) 71 (100), 57 (22), 43 (70), $[\alpha]^{25}_D$ = −15.1° ($CDCl_3$, *c* 4.0); IR (neat) 2960, 2920, 1785, 1750, 1715, 1145, 1080 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.18; H, 6.64.

A solution of (*R*)-tetrahydro-4,4-dimethyl-2-oxo-3-furanyl 3-oxobutanoate (10.1 g, 46.9 mmol) in dry acetonitrile (150 mL) was prepared and cooled to 0 °C. *p*-ABSA (11.8 g, 49.3 mmol) was added followed by Et_3N (6.25 mL, 44.8 mmol) with stirring, giving a tan precipitate. The reaction mixture was stirred for 1 h, and NH_4Cl (saturated aqueous 10 mL) was added. The reaction mixture was filtered, and the precipitate washed with 1:1 petroleum ether/Et_2O. To the filtrate was added water (400 mL), and the layers were separated. The aqueous layer extracted with CH_2Cl_2 (3 × 100 mL), and the organic layers were combined, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was triturated with 1:1 petroleum ether/Et_2O and then chromatographed (1:1 petroleum ether/Et_2O) to give the title product as a colorless solid. Recrystallization from Et_2O/petroleum ether gave pure colorless solid (mp = 96−97 °C). Yield: 9.12 g (38.0 mmol, 81%, 61% overall). ^1H NMR (200 MHz, $CDCl_3$) δ 5.46 (s, 1H), 4.08 (s, 2H), 2.50 (s, 3H), 1.26 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 189.2, 171.7, 160.2, 85.9, 76.1, 75.6, 40.1, 28.3, 22.9, 19.8; IR (neat) 2960, 2135, 1775, 1720, 1640, 1095 cm^{-1}; $[\alpha]^{25}_D$ = +4.6° ($CDCl_3$, *c* 2.29). Anal. Calcd for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.05; N, 11.66. Found: C, 49.96; H, 4.99; N, 11.66.

(1*S*)-2-Ethoxy-1-methyl-2-oxoethyl 2-Diazo-3-butenoate[6a] (18a). A solution of **17a** (23.0 g, 101 mmol) in absolute ethanol (125 mL) was prepared and cooled to 0 °C. Sodium borohydride (4.25 g, 112 mmol) was added in portions with stirring over 10 min. After 2 h, the reaction mixture was poured into 500 mL of cold NH_4Cl (saturated aqueous), and the mixture was extracted with CH_2Cl_2 (4 × 150 mL). The organic layers were combined and back-extracted with 150 mL of brine, dried ($MgSO_4$), and the solvent evaporated at 25 °C under reduced pressure to give a light yellow oil.[26]

The oil was dissolved in dry CH_2Cl_2 (125 mL), and triethylamine (75 mL, 538 mmol) was added. The solution was cooled to 0 °C in an ice bath, and a solution of $POCl_3$ (21 mL, 0.23 mol) in CH_2Cl_2, (10 mL) was added dropwise with stirring over 15 min. The mixture was stirred overnight while slowly warming to room temperature. The reaction was then slowly added to cold H_2O (500 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The organic layers were combined and washed with cold $NaHCO_3$ (saturated aqueous 250 mL) followed by cold brine (400 mL). The solvent was then evaporated under reduced presure to give a brown oil. The crude product was triturated with 4:1 petroleum ether/Et_2O and then chromatographed (4:1 petroleum ether/Et_2O) to give the title compound as a yellow-orange oil. Yield: 15.0 g (70.7 mmol, 70%). Once characterized (^1H NMR), the product can be stored for several weeks *in solution* at −20 °C without decomposition. ^1H NMR (200 MHz, $CDCl_3$) δ 6.09 (dd, J = 17.4, 11.0 Hz, 1H), 5.09 (q, J = 7.1 Hz, 1H), 5.04 (d, J = 11.0 Hz, 1H), 4.80 (d, J = 17.4 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 1.43 (d, J = 7.1 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.4, 163.9, 120.0, 107.6, 69.0, 61.3, 52.2, 16.8, 13.9; IR (neat) 2975, 2080, 1740, 1695, 1610, 1100 cm^{-1}; $[\alpha]^{25}_D$ = +40.5° ($CDCl_3$, *c* 2.32). Due to lack of stability, elemental analysis was not attempted on **18a**.

(Tetrahydro-4,4-dimethyl-2-oxo-3-furanyl) 2-Diazo-3-butenoate[6a] (18b). To a solution of **17b** (1.00 g, 4.16 mmol) in THF (75 mL) at 0 °C was added lithium tri-*tert*-butoxyaluminum hydride (3.18 g, 12.51 mmol). After 1 h, NH_4Cl (saturated aqueous 10 mL) was added, and the aluminum salts were removed by filtration through Celite. The filtrate was then poured into water (300 mL), extracted with $CHCl_3$ (4 × 100 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give a yellow oil (1.16 g). The oil was redissolved in freshly distilled CH_2Cl_2 (50 mL), and Et_3N (2.5 mL, 17.9 mmol) was added. The mixture was stirred under argon at −20 °C for 10 min, and freshly distilled $POCl_3$ (0.50 mL, 5.4 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 10 min. The mixture was allowed to warm to rt and left to stir for 24 h. The reaction mixture was poured into ice−water (500 mL), extracted with CH_2Cl_2 (3 × 100 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give a red oil. The

crude product was purified by silica gel chromatography (column washed prior to use with 5% Et_3N in petroleum ether to remove acidic sites) using 4:1 petroleum ether/Et_2O to give the title compound as a yellow oil. Yield: 307 mg (1.37 mmol, 33%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.17 (dd, J = 17.4, 11.0 Hz, 1H), 5.47 (s, 1H), 5.18 (d, J = 11.0 Hz, 1H), 4.93 (d, J = 17.4 Hz, 1H), 4.07 (s, 2H), 1.24 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.9, 163.1, 119.4, 108.1, 75.6, 75.2, 39.9, 22.4, 19.4; IR (neat) 2960, 2920, 2090, 1780, 1700, 1300, 1115 cm^{-1}; $[\alpha]^{25}_D$ = +5.70° ($CDCl_3$, *c* 1.08). Due to lack of stability, elemental analysis was not attempted on **18b**.

(1*S*)-2-Ethoxy-1-methyl-2-oxoethyl (1*R*,5*R*)-8-[(1,1-Dimethylethoxy)carbonyl]-8-azabicyclo[3.2.1]octa-2,6-diene-2-carboxylate (20a) ($Rh(OOct)_4$, 37.0 g, 75% yield, 66% de). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.62 (br s, 1H), 6.43 (br s, 1H), 5.92 (br d, J = 2.9 Hz, 1H), 5.10 (q, J = 7.0 Hz, 1H), 4.99 (br s, 1H), 4.60 (br s, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.05 - 2.60 (br m, 1H), 1.91 (br dd, J = 19.8, 3.4 Hz, 1H), 1.50 (d, J = 7.0 Hz, 3H), 1.41 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H); ^{1}H NMR (200 MHz, toluene-d_8, 95 °C) δ 6.64 (br s, 1H), 6.46 (dd, J = 6.1, 2.5 Hz, 0.17H, minor diastereomer), 6.41 (dd, J = 6.1, 2.5 Hz, 0.83H, major diastereomer), 5.71 (dd, J = 6.1, 2.5 Hz, 1H), 5.39 (br s, 1H), 5.32 (q, J = 7.0 Hz, 1H), 4.62 (br s, 1H), 4.15 (q, J = 7.1 Hz, 2H), 2.85 (br d, J = 20 Hz, 1H), 1.61 (br dd, 1H, J = 20, 3.7 Hz), 1.60 (s, 9H), 1.52 (d, J = 7.0 Hz, 1H), 1.19 (t, J = 7.1 Hz, 3H); IR (neat) 2965, 1710, 1620, 1440, 1365, 1090 cm^{-1}; $[\alpha]^{25}_D$ = +33.8° ($CHCl_3$, *c* 2.32). Anal. Calcd for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.93. Found: C, 61.63; H, 7.22; N, 3.93.

(1*S*)-2-Ethoxy-1-methyl-2-oxoethyl (1*R*,5*R*)-8-[(1,1-Dimethylethoxy)carbonyl]-3-[(1,1-dimethylethoxy)siloxy]-8-azabicyclo[3.2.1]octa-2,6-diene-2-carboxylate (21a). ($Rh_2(OOct)_4$, 9:1−4:1 petroleum ether/Et_2O, 1.45 g, 64% yield, 66% de). ^{1}H NMR (500 MHz, toluene-d_8, 95 °C) δ 6.42 (br s, 0.17H, minor diastereomer), 6.30 (dd, J = 5.7, 1.5 Hz, 0.83H, major diastereomer), 5.54 (dd, J = 5.7, 2.4 Hz, 1H), 5.35 (br s, 1H), 5.14 (q, J = 7.0 Hz, 1H), 4.50 (br s, 1H), 3.96 (q, J = 7.2 Hz, 2H), 2.84 (br d, J = 18.0 Hz, 1H), 1.56 (d, J = 18.0 Hz, 1H), 1.45 (s, 9H), 1.33 (d, J = 7.0 Hz, 3H), 1.01 (t, J = 7.2 Hz, 3H), 0.93 (s, 9H), 0.19 (s, 3H), 0.15 (s, 3H); IR (neat) 2984, 2943, 2855, 1760, 1714, 1604, 1374, 1262 cm^{-1}. Anal. Calcd for $C_{24}H_{39}NO_7Si$: C, 59.85; H, 8.16; N, 2.91. Found: C, 59.75; H, 8.14; N, 2.80.

(3*R*)-Tetrahydro-4,4-dimethyl-2-oxo-3-furanyl (1*S*,5*S*)-8-[(1,1-Dimethylethoxy)carbonyl]-8-azabicyclo[3.2.1]octa-2,6-diene-2-carboxylate (22a). ($Rh_2(OOct)_4$, 9:1−1:1 petroleum ether/Et_2O, 21 mg, 64% yield, 69% de). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.64 (br s, 1H), 6.39 (br s, 1H), 5.92 (br s, 1H), 5.37 (s, 1H), 4.96 (br s, 1H), 4.59 (br s, 1H), 4.01 (s, 2H), 2.90 (br d, J = 24 Hz, 1H), 1.89 (br dd, J = 20.1, 3.3 Hz, 1H), 1.37 (s, 9H), 1.18 (s, 3H), 1.07 (s, 3H); ^{1}H NMR (200 MHz, toluene-d_8, 95 °C) δ 6.66 (br s, 1H), 6.44 (dd, J = 6.1, 2.4 Hz, 0.16H, minor diastereomer), 6.35 (dd, J = 6.1, 2.4 Hz, 0.84H, major diastereomer), 5.68 (dd, J = 6.1, 2.4 Hz, 1H), 5.33 (br s, 2H), 4.60 (br s, 1H), 3.68 (br s, 2H), 2.82 (br d, J = 20 Hz, 1H), 1.58 (s, 9H), 1.56 (br dd, J = 17.5, 3.9 Hz, 1H), 0.98 (s, 3H), 0.92 (s, 3H); $[\alpha]^{25}_D$ = −14.0° ($CHCl_3$, *c* 1.83). HRMS calcd for $C_{19}H_{25}NO_6$ 363.1682; found 363.1691.

(3*R*)-Tetrahydro-4,4-dimethyl-2-oxo-3-furanyl (1*S*,5*S*)-8-(1,1-Dimethyl-ethoxycarbonyl)-3-[(1,1-dimethylethoxy)siloxy]-8-azabicyclo[3.2.1]octa-2,6-diene-2-carboxylate (23a) ($Rh_2(OOct)_4$, 9:1−4:1 petroleum ether/Et_2O, 4.08 g, 66% yield, 68% de). ^{1}H NMR (500 MHz, toluene-d_8, 95 °C) δ 6.41 (dd, J = 6.1, 2.4 Hz, 0.16H, minor diastereomer), 6.25 (dd, J = 6.0, 2.3 Hz, 0.84H, major diastereomer), 5.56 (dd, J = 6.0, 2.6 Hz, 1H), 5.30 (br s, 1H), 5.15 (s, 1H), 4.50 (br d, J = 2.3 Hz, 1H), 3.43 (d, J = 8.9 Hz, 1H), 3.29 (d, J = 8.9 Hz, 1H), 2.88 (br d, J = 18.0 Hz, 1H), 1.57 (d, J = 18.0 Hz, 1H), 1.45 (s, 9H), 0.93 (s, 9H), 0.79 (s, 3H), 0.74 (s, 3H), 0.21 (s, 3H), 0.16 (s, 3H); IR (neat) 2966, 2934, 2857, 1797, 1724, 1698, 1600, 1471, 1367, 1253 cm^{-1}. Anal. Calcd for $C_{25}H_{39}NO_7Si$: C, 60.82; H, 7.96; N, 2.84. Found: C, 60.71; H, 8.01; N, 2.76.

(1*S*)-2-Ethoxy-1-methyl-2-oxoethyl (1*R*,5*S*)-8-[(1,1-Dimethylethoxy)carbonyl]-5-methyl-8-azabicyclo[3.2.1]octa-2-ene-2-carboxylate (24b). A Parr hydrogenator flask was charged with a solution of **20b** (0.937 g, 2.55 mmol) and $(PPh_3)_3RhCl$ (47 mg, 0.051 mmol, 2 mol %) in 45 mL absolute ethanol. The flask was pressurized to 45 psi with hydrogen and agitated for 24 h. The solvent was then removed under reduced pressure to give the crude product, which was purified by column chromatography (4:1−1:1 petroleum ether/Et_2O) to give the title compound as an oil. Yield: 0.78 g (2.12 mmol, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (m, 1H), 5.08 (q, J = 7.1 Hz, 1H), 4.98 (d, J = 6.0 Hz, 1H), 4.50 (q, J = 7.1 Hz, 2H), 2.87 (br d, J = 19.5 Hz, 1H), 2.01 (dd J = 19.5, 4.2 Hz, 1H), 1.62−2.02 (m, 4H), 1.59 (s, 3H), 1.52 (d, J = 7.1 Hz, 3H), 1.38 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H). Anal. Calcd for $C_{19}H_{29}NO_6$: C, 62.11; H, 7.96; N, 3.81. Found: C, 61.98; H, 7.92; N, 3.74.

All of the other tropanes were hydrogenated using a similar procedure except for **20h**, where Pd/C was used. Tropane **20c** was not further derivatized. Purification and full characterization were carried out on **24d** and **24h**. Characterization data, solvent for chromatographic purification, amount of product and reaction yields are provided in the Supporting Information.

Methyl (1*R*,5*S*)-8-[(1,1-Dimethylethoxy)carbonyl]-8-azabicyclo[3.2.1]octa-2-ene-2-carboxylate (25a). To a solution of NaOMe (77.6 g, 1.44 mol) in dry methanol (850 mL) at 0 °C was added a solution of **24a** (67 g, 0.18 mol) in methanol (200 mL) over 15 min. The reaction was stirred for 1 h, and the mixture was then concentrated under reduced pressure. The mixture was added to NH_4Cl (saturated aqueous 1L), and the aqueous solution was extracted with Et_2O (3 × 300 mL). The organic extracts were combined, back-extracted with brine (500 mL), dried ($MgSO_4$), and filtered through a pad of silica gel. The filtrate was evaporated to give the title compound as an orange oil. Yield: 43.5 g (0.163 mol, 90%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.74 (br t, J = 2.8 Hz, 1H), 4.79 (br d, J = 2.8 Hz, 1H), 4.30 (br s, 1H), 3.73 (s, 3H), 3.00−2.65 (br m, 1H), 2.19−1.44 (m, 5H), 1.41 (s, 9H); IR (neat) 2870, 1690, 1245, 1160, 1095, 975, 875, 755 cm^{-1}; $[\alpha]^{25}_D$ = −47.2° ($CHCl_3$, *c* 2.45); MS *m/e* (relative intensity) 211 (31), 138 (47), 57 (100). Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.66; H, 7.95; N, 5.29.

Methanolysis was carried out on all of the other tropanes using a similar procedure. Purification and full characterization was carried out on **25b**, **25g**, and **25h**. Chromatography solvents, amounts, and reaction yields are provided in the Supporting Information.

(1*R*,5*S*)-[(1,1-Dimethylethoxy)carbonyl]-8-azabicyclo-[3.2.1]octa-2-ene-2-carboxylic Acid (26a). A solution of **25a** (19.9 g, 74.4 mmol) and $LiOH·H_2O$ (4.7 g, 0.11 mol) in methanol/water (3:1, 200 mL) was heated under reflux for 7 h. The mixture was cooled to rt, poured into water (400 mL), and extracted with CH_2Cl_2 (75 mL). The aqueous solution was slowly acidified with concd HCl to pH 2,[27] and then extracted with CH_2Cl_2 (3 × 125 mL). The organic extracts were combined, dried ($MgSO_4$), and evaporated to give **26a** as a tan solid (mp 154−158 °C). Yield: 18.1 g (71.5 mmol, 96%). ^{1}H NMR ($CDCl_3$) δ 6.89 (br s, 1H), 4.80 (br s, 1H), 4.38−4.28 (br d, 1H), 3.00−2.90 (br s, 1H), 2.20 (m, 1H), 2.12−1.80 (m, 3H), 1.60 (br s, 1H), 1.45 (s, 9H). IR (neat) 3600−2400 (broad), 1700, 1696, 1636, 1419, 1411, 1394 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.52; H, 7.59; N, 5.44.

(1*R*,5*S*)-2-Acetyl-[(1,1-dimethylethoxy)carbonyl]-8-azabicyclo[3.2.1]octa-2-ene[4a] (28a). A solution of **26a** (2.54 g, 10.0 mmol) in 50 mL of dry CH_2Cl_2 was prepared, and $SOCl_2$ (1.1 mL, 15 mmol) was added. The mixture was heated to reflux for 1 h. After the reaction cooled to rt, the solvent was evaporated, and excess $SOCl_2$ was removed under vacuum to give the acid chloride (**27a**), which was characterized by ^{1}H NMR and used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.20 (br s, 1H), 4.83 (br s, 1H), 4.36 (br s, 1H), 3.0 (br s, 1H), 2.25−2.05 (m, 3H), 1.92 (m, 1H), 1.59−1.65 (m, 1H), 1.43 (s, 9H).

A 250 mL, three-necked flask was charged with $CuBr·SMe_2$ (2.45 g, 11.9 mmol) and cooled to −78 °C under argon. With mechanical stirring, a solution of MeMgBr in Et_2O (Aldrich, 10 mL, 30 mmol) was added, giving a yellow paste. A solution of **27a** in 50 mL of dry THF was added dropwise over 30 min via a pressure-equalized addition funnel with stirring. The reaction was stirred for 2 h at −78 °C and then quenched with

75 mL of NH_4Cl (saturated aqueous). The reaction was warmed to rt and 100 mL of Et_2O added. The mixture was filtered, and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 50 mL). The organic layers were combined, back-extracted with 100 mL of brine, and dried ($MgSO_4$), and the solvent evaporated. The crude product was chromatographed (2:1 petroleum ether/Et_2O) to give the title compound as a yellow oil. Yield: 1.88 g (7.47 mmol, 75% from **26a**).

(1*R*,5*S*)-[(1,1-Dimethylethoxy)carbonyl]-2-propionyl-8-azabicyclo[3.2.1]octa-2-ene[2a] (29a). A sample of **26a** (10.1 g, 40.0 mmol) was converted to the acid chloride (**27a**) as described above. A solution of **27a** in 100 mL dry of THF was prepared, and $Pd_2(dba)_3$ (550 mg, 0.600 mmol, 1.5 mol %) was added. The reaction mixture was cooled to 0 °C, and a solution of diethylzinc in hexanes (Aldrich, 40 mL, 40 mmol) was added with stirring. After 30 min, the reaction was quenched at 0 °C by addition of 300 mL of $NaHCO_3$ (saturated aqueous) The mixture was stirred for 1 h, and Et_2O (300 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 150 mL). The organic layers were combined, back-extracted with 150 mL of brine, dried ($MgSO_4$), and evaporated. The crude product was purified by column chromatography (2:1 petroleum ether/Et_2O) to give the title compound as a yellow oil. Yield: 5.0 g (18.8 mmol, 47% overall from **26a**).

Methyl (1*R*,5*S*)-8-Azabicyclo[3.2.1]octa-2-ene-2-carboxylate[7] (30a). A solution of **25a** (4.02 g, 15.0 mmol) in dry CH_2Cl_2 (40 mL) was prepared and TFA (12 mL, 156 mmol, 10 equiv) added. The reaction was stirred for 1 h and poured into H_2O (40 mL). The layers were separated, and the organic layer was washed with H_2O (30 mL). The aqueous layers were combined, and brine (40 mL) was added. The solution was basified with concd NH_4OH (aqueous) and extracted with CH_2Cl_2 (4 × 50 mL). The solution was dried ($MgSO_4$), and evaporated to give the title compound as a light yellow oil. Yield: 2.08 g (12.4 mmol, 83%).

The other tropanes were deprotected using a similar procedure. Purification was achieved via either column chromatography, Kugelrohr distillation, or recrystallization. Chromatography solvents, amounts, and overall yields from the starting tropanes **20** are given in parentheses.

Methyl (1*R*,5*S*)-5-Methyl-8-azabicyclo[3.2.1]octa-2-ene-2-carboxylate (30b) (purified by Kugelrohr distillation, 96 °C, 0.75 torr; 0.21 g, 49% overall from **20b**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69 (dd, J = 4.5, 2.9 Hz, 1H), 4.10 (d, J = 5.9 Hz, 1H), 3.66 (s, 3H), 2.30 (br d, J = 19.3 Hz, 1H), 2.06 (dd, J = 19.3, 4.5 Hz, 1H), 1.90 (m, 1H), 1.82 (m, 1H), 1.45−1.65 (m, 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 137.8, 136.9, 57.5, 54.8, 51.2, 42.7, 36.5, 36.4, 27.0; IR (neat) 3302, 3229, 2955, 1715, 1647, 1440, 1274, 1239 cm^{-1}. Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.26; H, 8.35; N, 7.73. Found: C, 66.00; H, 8.39; N, 7.55.

Methyl (1*R*,5*S*)-5-Phenyl-8-azabicyclo[3.2.1]octa-2,6-diene-2-carboxylate (30d) (crystallized from hexane/Et_2O, 1.11 g, 69% overall from **20d**). Mp = 84−87 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 7.7 Hz, 2H), 7.36 (t, J = 7.7 Hz, 3H), 6.83 (dd, J = 4.2, 2.7 Hz, 1H), 4.38 (d, J = 5.5 Hz, 1H), 3.78 (s, 3H), 2.60 (br dd, J = 19.2, 2.7 Hz, 1H), 2.54 (dd, J = 19.2, 4.2 Hz, 1H), 2.02−2.20 (m, 4H), 1.73 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2, 147.8, 137.9, 136.5, 126.6, 124.9, 83.1, 54.5, 51.4, 44.0, 37.7, 36.0; IR (neat) 3416, 3064, 2950, 1714, 1652, 1440, 1367, 1238, 1088 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.13; H, 7.08; N, 5.69.

Methyl (1*R*,5*S*)-5-Acetyl-8-azabicyclo[3.2.1]octa-2-ene-2-carboxylate (30e) (crystallized from hexane/Et_2O, 0.43 g, 52% overall yield from **20e**). Mp = 64−68 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (dd, J = 4.4, 2.8 Hz, 1H), 4.22 (d, J = 5.5 Hz, 1H), 3.69 (s, 3H), 2.54 (br d, J = 19.2 Hz, 1H), 2.36 (dd, J = 19.2, 4.4 Hz, 1H), 2.21 (s, 3H), 1.85−2.05 (m, 4H), 1.72 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.0, 165.6, 137.7, 135.4, 68.6, 54.8, 51.5, 37.3, 35.7, 34.0, 24.9; IR (neat) 3297, 2950, 2872, 1709, 1651, 1440, 1357, 1248, 1093 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.22; H, 7.27; N, 6.62.

Methyl (1*R*,5*R*,6*R*)-6-Methyl-8-azabicyclo[3.2.1]octa-2-ene-2-carboxylate (30g) (19:1−9:1 Et_2O/Et_3N, 0.43 g, 60% overall from **20g**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (m, 1H), 4.02 (d, J = 6.4 Hz, 1H), 3.73 (s, 3H), 3.55 (t, J = 6.0 Hz, 1H), 2.43−2.48 (m, 2H), 2.22−2.78 (m, 2H), 1.74 (br s, 1H), 1.34 (dd, J = 12.2, 4.3 Hz, 1H), 1.03 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 140.1, 136.4, 56.1, 52.9, 51.5, 42.3, 36.2, 29.4, 18.1; IR (neat) 3307, 3224, 2955, 2872, 1714, 1647, 1445, 1378, 1274, 1171 cm^{-1}. Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.17; H, 8.40; N, 7.63. The triplet at δ 3.55 for the bridgehead proton confirms the *endo*-stereochemistry of the methyl group.

Methyl (1*R*,5*R*,7*R*)-12-Azatricyclo[5.4.1$^{1.5}$.0$^{1.7}$]dodeca-3-ene-4-carboxylate (30h) (9:1 hexane/EtOAc, 0.35 g, 57% overall from **20h**). ^{1}H (300 MHz, $CDCl_3$) δ 6.63 (d, J = 3.7 Hz, 1H), 4.12 (dd, J = 7.5, 1.4 Hz, 1H), 3.69 (s, 3H), 2.59 (dd, J = 20.5, 3.6 Hz, 1H), 2.24 (ddd, J = 12.2, 10.6, 7.4 Hz, 1H), 2.07 (ddd, J = 20.5, 4.0, 1.4 Hz, 1H), 1.81−1.62 (m, 6H), 1.49−1.36 (m, 2H), 1.32−1.22 (m, 2H), 1.19−1.15 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.7, 143.0, 137.0, 59.0, 51.3, 51.2, 49.6, 38.8, 38.1, 33.1, 26.2, 25.2, 21.0; IR (neat) 3297, 3219, 2939, 2851, 1708, 1652, 1434, 1258, 1191, 1072 cm^{-1}; MS *m*/*e* 221 (M^+) (100), 220 (66), 206 (28), 192 (10), 190 (13), 178 (25), 164 (47), 162 (41), 161 (43), 151 (28), 106 (7). HRMS calcd for $C_{13}H_{19}NO_2$ 221.1415; found: 221.1398.

(1*R*,5*S*)-2-Acetyl-8-azabicyclo[3.2.1]octa-2-ene[4a,7] (31a). Prepared from **28a** in 99% yield using the general BOC-deprotection procedure described above.

(1*R*,5*S*)-2-Propionyl-8-azabicyclo[3.2.1]octa-2-ene[2a] (32a). Prepared from **29a** in quantitative yield using the general BOC-deprotection procedure described above.

Conversion of 21a to 24a. A sample of **21a** was first hydrogenated using the general hydrogenation procedure described above to give (1*S*)-2-ethoxy-1-methyl-2-oxoethyl (1*R*,5*R*)-8-[(1,1-dimethylethoxy)carbonyl]-3-[(1,1-dimethylethoxy)siloxy]-8-azabicyclo[3.2.1]octa-2-ene-2-carboxylate, which was then desilyated using the following procedure: To a solution of the above tropane (3.38 g, 7.0 mmol) in dry THF (25 mL) was added a 1 M solution of TBAF (7.0 mL, 7.0 mmol) in THF dropwise. The mixture was stirred at rt for 15 min, and H_2O (100 mL) was added. The mixture was extracted with Et_2O (3 × 100 mL), and the organic extracts were combined, dried ($MgSO_4$), and evaporated. The crude product was purified by column chromatography (1:1 petroleum ether/Et_2O) to give the desired product as a mixture of tautomers. Yield: 1.92 g (5.20 mmol, 74%).

To a solution of the above material (2.44 g, 6.61 mmol) in THF (25 mL) was added a solution of NaHMDS (1.0M, 7.0 mL, 7.0 mmol) in THF at −78 °C. After stirring for 30 min at −78 °C, the mixture was warmed to rt. *N*-Phenyltrifluoromethanesulfonimide (2.36 g, 6.61 mmol) was added all at once, and the mixture was stirred overnight. The reaction was diluted with NH_4Cl (saturated aqueous) and H_2O and then extracted with CH_2Cl_2 (3 × 150 mL). The organic extracts were combined, dried ($MgSO_4$), and evaporated to give the crude 3-triflato derivative, which was used for the next step without purification.

To a mixture of the crude triflate derivative (1.20 g, 2.39 mmol), tri-*n*-butylamine (2.0 mL, 8.64 mmol), triphenylphosphine (31 mg, 0.012 mmol), and $PdCl_2$ (12 mg, 0.068 mmol) in DMF (15 mL) was added 88% formic acid (0.24 mL, 5.8 mmol) at rt. The mixture was heated for 2 h at 60 °C. The reaction was cooled to rt, and EtOAc and H_2O were added. The organic layer was separated, washed with H_2O, dried ($MgSO_4$), and evaporated to give crude **24a**, which was purified by column chromatography (9:1−7:3 petroleum ether/Et_2O). Tropane **24a** was subsequently converted to **30a**, whose absolute stereochemistry was confirmed via conversion to its Mosher amide.

Synthesis of Tropane/Di-*p*-Toluoyl Tartrate Salts. General Procedure. A solution of the enriched tropane in absolute ethanol (15−25 mL/g) was prepared and the desired enantiomer of di-*p*-toluoyl tartaric acid (1.1 equiv) added with stirring. The reaction mixture was gently warmed to produce a homogenous solution, and the solvent was evaporated. The resulting solid was triturated with Et_2O, filtered, washed with Et_2O, and dried *in vacuo*, producing the diastereomeric salt

as an off-white powder in 75−95% yield. The diastereomeric purity was determined by integration of the diastereomeric H(3) resonances in the ^{1}H NMR spectrum (500 MHz, DMSO-d_6). The pure major diastereomer was obtained by performing two or three successive recrystallizations by dissolving the salt in a minimum amount of refluxing absolute ethanol and allowing the solution to slowly cool to room temperature while stirring. The crystallization can be seeded with a sample of pure diastereomeric salt if available. After the slurry had completely cooled to room temperature (∼2 h), it was filtered, washed with a small amount of cold absolute ethanol followed by Et_2O, and dried *in vacuo*. The recovery yield of resolved salt was typically approximately 40−55% after three crystallizations.

The enantiomerically pure tropane was recovered by dissolving the salt in concentrated NH_4OH (aqueous) (10−15 mL/g of salt) and extracting with CH_2Cl_2 (3×). The organic layers were combined, dried ($MgSO_4$), and evaporated to give the enantiomerically pure tropane in ∼90% yield.

Methyl (1*R*,5*S*)-8-Azabicyclo[3.2.1]octa-2-ene-2-carboxylate/Di-*p*-toluoyl-D-tartrate (38a). Mp = 154−160 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.82 (d, J = 7.9 Hz, 4H), 7.31 (d, J = 8.2 Hz, 4H), 6.78 (dd, J = 3.5, 3.5 Hz, 1H), 5.60 (s, 2H), 4.44 (d, J = 5.2 Hz, 1H), 4.02 (br t, 1H), 3.70 (s, 3H), 2.76 (d, J = 19.8 Hz, 1H), 2.36 (s, 6H), 2.27 (dd, J = 20.1, 4.3 Hz, 1H), 2.08−1.88 (m, 3H), 1.60−1.68 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.85, 165.32, 164.26, 144.01, 136.99, 131.36, 129.58, 129.48, 127.27, 72.51, 51.88 (2 carbons), 51.46, 32.99, 32.85, 27.54, 21.04. Anal. Calcd for $C_{29}H_{31}NO_{10}\cdot 0.5H_2O$: C, 61.92; H, 5.73; N, 2.49. Found: C, 61.80; H, 6.05; N, 2.27.

(1*R*,5*S*)-2-Acetyl-8-azabicyclo[3.2.1]octa-2-ene/Di-*p*-toluoyl-D-tartrate (39a). Mp = 161−2 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.80 (d, J = 8.5 Hz, 4H), 7.29 (d, J = 9.0 Hz, 4H), 6.93 (dd, J = 3.4, 3.4 Hz, 1H), 5.59 (s, 2H), 4.52 (d, J = 6.0 Hz, 1H), 4.03 (dd, J = 6.0, 5.5 Hz, 1H), 2.81 (d, J = 20.5 Hz, 1H), 2.34 (s, 6H), 2.23 (s, 3H), 2.22 (dd, 1H, partially overlapped), 2.10−1.95 (m, 2H), 1.80 (m, 1H), 1.63 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 196.0, 168.6, 165.3, 144.1, 139.7, 137.8, 129.6, 129.5, 127.19, 51.7, 50.8, 33.1, 32.6, 27.6, 24.8, 21.0. Anal. Calcd for $C_{29}H_{31}NO_9\cdot 0.5H_2O$: C, 63.73; H, 5.90; N, 2.56. Found: C, 63.62; H, 6.21; N, 2.46.

(1*R*,5*S*)-2-Propionyl-8-azabicyclo[3.2.1]octa-2-ene/Di-*p*-toluoyl-D-tartrate (40a). Mp = 126.5−129.5 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.79 (d, J = 8.1 Hz, 4H), 7.28 (d, J = 8.1 Hz, 4H), 6.93 (dd, J = 3.7, 3.4 Hz, 1H), 5.58 (s, 2H), 4.52 (d, J = 5.8 Hz, 1H), 4.03 (dd, J = 6.1, 5.5 Hz, 1H), 2.81 (d, J = 20.1 Hz, 1H), 2.65 (q, J = 7.3 Hz, 2H), 2.34 (s, 6H), 2.31 (dd, J = 4.5, 20.8 Hz, 1H), 2.15−1.92 (m, 2H), 1.81 (m, 1H), 1.65 (m, 1H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 198.6, 168.6, 165.3, 144.0, 139.1, 136.4, 129.53, 129.46, 127.2, 71.9, 56.0, 51.8, 51.0, 33.1, 32.7, 29.4, 27.6, 21.0, 7.9. Anal. Calcd for $C_{30}H_{33}NO_9\cdot 0.5H_2O$: C, 64.28; H, 6.11; N, 2.50. Found: C, 64.03; H, 6.19; N, 2.42.

Synthesis of Mosher Amides. General Procedure. In a 1 dram vial, a solution of tropane (15−25 mg) and diisopropylethylamine (2.5−3.5 equiv) was prepared in 0.5 mL of dry CH_2Cl_2. (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (Aldrich, 1.5−2 equiv) was added, and a stream of argon was blown over the reaction mixture for 30 s. The reaction was allowed to stand for 24−48 h, diluted with CH_2Cl_2 (5 mL), and added to 10 mL of NH_4Cl (saturated aqueous). The mixture was stirred for 30 min and the layers were separated. The aqueous solution was extracted with CH_2Cl_2 (3 mL), and the organic layers were combined, dried ($MgSO_4$), and filtered through a silica plug in a 15 mL medium porosity frit. The frit was washed with Et_2O (2 × 5 mL), and the filtrate was evaporated to give the *R*-Mosher amide, which was characterized by ^{1}H NMR (500 MHz). The *S*-Mosher amide was prepared by repeating the reaction conditions with the *R*-acid chloride. ^{1}H NMR data for the Mosher amides studied is presented in Tables 3 and 4.

(−)-Anhydroecgonine Methyl Ester[6a,7] (33a). A solution of enantiomerically pure **30a** (219 mg, 1.31 mmol) was prepared in 20 mL of dry acetonitrile. An aqueous solution of HCHO (37%, 0.5 mL, 6 mmol) was added and the solution stirred for 5 min. $Na(CN)BH_3$ (128 mg, 2.0 mmol) was added with stirring, and the reaction was stirred for 1 h. The reaction was quenched by slow addition of 20 mL of glacial HOAc over 1 h. The reaction was diluted with H_2O (50 mL), neutralized by addition of $NaHCO_3$ (s), and basified to pH 12 with 1 M NaOH (aqueous). The aqueous solution was extracted with CH_2Cl_2 (4 × 60 mL), and the organic extracts were combined, dried ($MgSO_4$), and evaporated to give the crude product, which was chromatographed (10% Et_3N in Et_2O) to give the title compound as a colorless oil. Yield: 177 mg (0.977 mmol, 74%). Optical rotation: $[\alpha]^{25}_D = -41.7°$ (*c* 1.50, CH_3OH), lit. $[\alpha]^{25}_D = -43°$.[5]

(−)-Ferruginine[7] (34a). Prepared from **31a** in 71% yield using a procedure similar to that used for the synthesis of **33a**. Optical rotation: $[\alpha]^{25}_D = -50.8°$ (*c* 0.94, $CHCl_3$), lit. $[\alpha]^{19}_D = -37°$.[28]

(1*R*,5*S*)-8-Methyl-2-propionyl-8-azabicyclo[3.2.1]octa-2-ene (35a). Prepared from **32a** in 79% yield using a procedure similar to that used for the synthesis of **33a**.

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Supporting Information Available: Experimental and characterization data of tropanes **20b**−**h**, **21b**, **21d**−**f**, **23d**, **23e**, **23h**, **24d**, **24h**, **25b**, **25g**, and **25h** as well as copies of ^{1}H NMR spectra of **4b**, **4d**, **4g**, **6**, **12**, **20h**, **22a**, **23h**, and **30h** (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(26) While the intermediate alcohol is not thermally stable, care must be taken to remove all of the ethanol before the elimination step. Typically, the crude oil was pumped under high vacuum (∼0.5 torr) for at least 30 min before the next step.

(27) Note that at lower pH, the BOC protecting group will be removed.

(28) Bick, I. R. C.; Gillard, J. W.; Leow, H. M. *Aust. J. Chem*. **1979**, *32*, 2537.