Asymmetric Induction in the Metal-Promoted [6π + 2π] Cycloaddition of Azepines. Application to the Construction of Tropane Alkaloids and the Total Synthesis of (+)-Ferruginine

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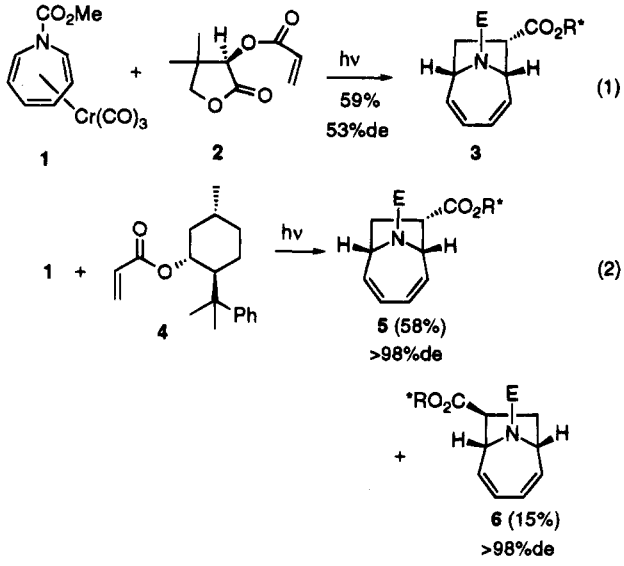
Received September 14, 1995

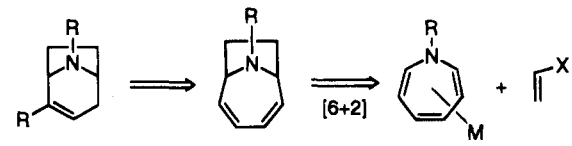
Asymmetric induction during transition metal-promoted higher-order cycloaddition represents a potentially effective method for rapid assembly of enantiomerically-enriched polycyclic systems that are amenable to conversion into a range of natural product targets.[1] Auxiliary-based induction during Cr(0)-mediated [6π + 2π] cycloaddition[2] of azepine derivatives would provide direct access to chiral, nonracemic homotropane products,[3] and subsequent conversion to the important tropane alkaloid ring system could be accomplished by employing appropriate ring-contraction technology (Scheme 1).[4,5]

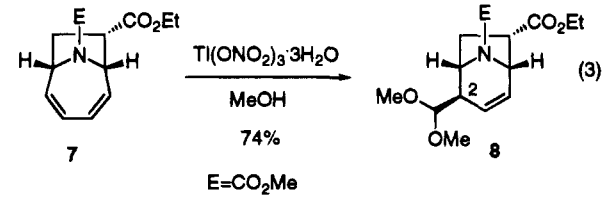
We disclose that good to excellent diastereoselection can be achieved during the [6 + 2] cycloaddition of tricarbonyl(*N*-(methoxycarbonyl)azepine)chromium(0) and that the resultant homotropane intermediates can be efficiently transformed into enantiomerically homogeneous tropane products via Tl(III)-mediated oxidative rearrangement.



Irradiation (Pyrex) of a solution of azepine complex **1**[6] with the acrylate derivative of (R)-(−)-pantolactone **2**[7] proceeded smoothly to afford the homotropane cycloadduct **3**[8] (59% yield, 53% de). In contrast, photocycloaddition of the same complex with (−)-8-phenylmenthyl acrylate (**4**)[9] gave the anticipated endo-adduct **5**[8] (58%) along with the unexpected exo-adduct **6**[8] (15%). Each isomeric species was produced in diastereomerically homogenous form as established by ^{1}H NMR. Since metal-promoted higher-order cycloaddition rarely proceeds through the exo-reaction channel, it is likely that the adduct **6** observed in this instance was produced by an epimerization of the initially formed endo isomer under the cycloaddition reaction conditions. It is noteworthy, however, that efforts to effect a similar isomerization of the major endo product **5** to the corresponding exo species under either acidic or basic conditions were futile.[10] Therefore, based on extant empirical data we cannot exclude the possibility that the normally disfavored exo-pathway is being followed to a minor extent in this particular transformation, although molecular modeling does not reveal any compeling steric factors to account for the formation of **6** during the cycloaddition event. The major diastereomers produced from both the pantolactone and 8-phenylmenthyl systems were shown to belong to the same enantiomeric series by reductive removal of the respective auxiliaries, and the absolute stereochemistry of these adducts was established by subsequent correlation with (+)-ferruginine (*vide infra*).

Scheme 1





The 1,3-diene function present in the cycloadducts **3**, **5**, and **6** represents a potentially serviceable handle for effecting the desired ring contraction to the tropane system; however, manipulation of these unsaturations in a regiocontrolled fashion could be problematic. The well-known McKillop–Taylor Tl(III)-oxidative rearrangement protocol offers a particularly attractive, one-step solution

(1) For a leading reference to Cr(0)-promoted cycloaddition reactions, see: Rigby, J. H. *Acc. Chem. Res.* **1993**, *26*, 579.

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(4) For leading references to tropane alkaloids, see: (a) Fodor, G.; Dharanipragada, R. *Nat. Prod. Rep.* **1994**, *11*, 443. (b) Lounasmaa, M. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1988; Vol. 33, pp 1–81. (c) Lounasmaa, M.; Tamminen, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1993; Vol. 44, p 1.

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(7) Poll, T.; Sobczak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett.* **1985**, *26*, 3095.

(8) This compound gave spectral (^{1}H NMR, ^{13}C NMR, IR) and analytical (combustion analysis and/or HRMS) data consistent with the assigned structure.

(9) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.

(10) To date, only a single example of a metal-promoted higher-order cycloaddition proceeding through what can be termed an *exo* transition state has been identified. However, this reaction occurred in a highly constrained intramolecular environment: Rigby, J. H.; Sandanayaka, V. P. *Tetrahedron Lett.* **1993**, *34*, 935.

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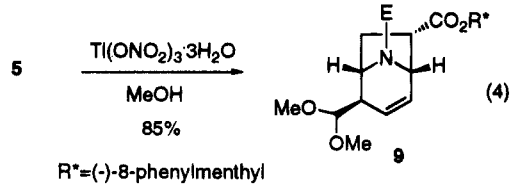
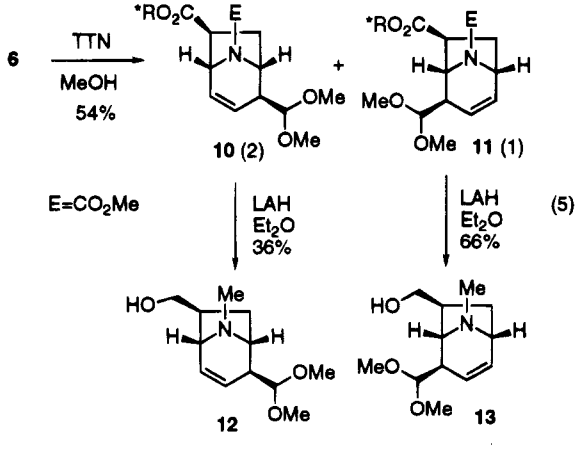
to this issue.[11] Unfortunately, the bulk of the existing literature dealing with this process suggests that conjugated dienes normally lead to simple 1,2- and 1,4-oxidation products rather than to bond reorganization.[11,12] However, one intriguing report of modestly efficient vinyl group migration during oxythallation of simple 1,3-dienes has appeared.[13] Despite the lack of precedent for the desired reaction pathway, the appeal of the method for solving our particular problem compelled us to perform a trial run on one of our substrates. In the event, racemic adduct **7**,[8] prepared from ethyl acrylate in 77% yield,[2] was exposed to thallium trinitrate (TTN) in MeOH, and to our delight *a single ring-contracted product* **8**[8] *was formed in very good yield* (eq 3). To the best of our knowledge this transformation represents the first example of an efficient Tl(III)-mediated oxidative rearrangement of a structurally elaborate diene system. The regiochemistry of the product was established by ^{1}H-homonuclear decoupling, and the C-2 stereochemistry was assigned on the basis of the small coupling observed between H-1 and H-2 ($J_{12} \approx$ O).

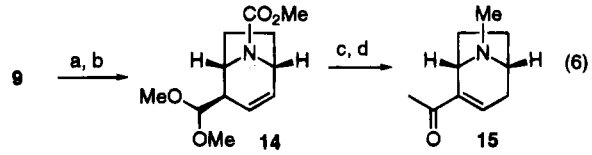
Treatment of enantiomerically pure cycloadduct **5** under identical reaction conditions provided a single, optically pure tropane product **9** in excellent yield.



Interestingly, epimeric diene **6** provided, under similar conditions, a 2:1 mixture of tropanes **10** and **11**, respectively, which were subsequently characterized as the corresponding *N*-methyl amino alcohols **12**[8] and **13**.[8] It is noteworthy that decarboxylation of **10** would give an intermediate in the natural cocaine enantiomeric series. The efficiency and selectivity of this ring contraction technology provides a rapid, one-step conversion of the readily available homotropane system into the important tropane series while retaining the enantiomeric purity that was established in the initial cycloaddition step.



The regioselectivity exhibited by these transformations appears to stem from the electron-withdrawing nature of the proximate alkoxycarbonyl group, which may be dictating the course of these reactions by forcing the initial oxythallation event to occur at the more remote (and more electron rich) alkene of the diene system. At this juncture it is unclear whether the bond reorganization occurs via vinyl group migration or by rearrangement of the nitrogen substituted carbon atom. Further exploration of these issues, as well as application of this method to other diene systems is currently underway.



a) LiOH, MeOH/H_2O (84%) b) $ClCO_2i$-Bu, N-Methylmorpholine; N-hydroxypyridine-2-thione, Na salt, TEA; t-BuSH, hv (49%) c) TFA, H_2O/acetone d) MeMgBr, Et_2O; $LiAlH_4$, Et_2O; Dess-Martin periodinane, CH_2Cl_2(28%).

Compound **9** represents an ideal enantiomerically pure building block for tropane alkaloid synthesis, and to illustrate this point, a total synthesis of (+)-ferruginine was performed. Smooth saponification of **9** followed by decarboxylation via the Barton thiohydroxamate ester protocol[14] afforded key intermediate **14**,[8] which was further subjected to a routine series of functional group interchanges that proceeded through the corresponding α,β-unsaturated aldehyde. This sequence of reactions afforded (+)-ferruginine (**15**) ($[\alpha]_D = +34.5$ ($CHCl_3$); lit.[15] $[\alpha]_D = +37$ ($CHCl_3$)) in good yield, and the ^{1}H NMR spectrum of the synthetic material was identical in all respects with that previously reported by Davies.[16a] While several syntheses of racemic **15** have been disclosed,[5c,16] this appears to be the first total synthesis of the natural product in optically pure form. The construction of (+)-ferruginine also establishes the absolute stereogenicity of the initial cycloadducts **3** and **5**.

The successful execution of a tandem Cr(0)-promoted [6 + 2] cycloaddition–Tl(III)-mediated oxidative rearrangement of N-substituted azepines affords a novel and efficient entry into tropane alkaloid building blocks that are appropriately functionalized for further elaboration into a range of natural and unnatural analogs. The capability of effecting the initial cycloaddition step in diastereoselective fashion makes the new methodology particularly suitable for constructing the tropane systems in optically pure form.

Acknowledgment. The authors thank the National Institutes of Health (GM-30771) for their support of this research.

Supporting Information Available: Experimental procedures and complete spectroscopic data for compounds **3** and **5**–**14** (9 pages).

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