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ASYMMETRIC SYNTHESIS OF THE TREMULANE SKELETON BY A TANDEM CYCLOPROPANATION/COPE REARRANGEMENT

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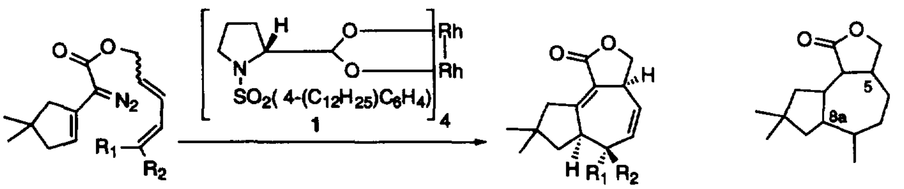
Abstract: A highly diastereoselective and enantioselective 3 + 4 annulation method for the synthesis of polycyclic systems was achieved in a two step sequence consisting of an asymmetric intramolecular cyclopropanation catalyzed by dirhodium(II) tetrakis((R)-N-(p-(dodecyl)phenylsulfonyl)prolinate) followed by a Cope rearrangement of the resulting divinylcyclopropane intermediate. Copyright © 1996 Elsevier Science Ltd

The 3+4 annulation strategy is a powerful convergent approach for the construction of seven-membered carbocycles.[1] For some time, we have been developing a highly stereoselective approach for the construction of seven-membered carbocycles by means of a tandem cyclopropanation/Cope rearrangement between rhodium-stabilized vinylcarbenoids and dienes.[2] The relative stereochemistry at three stereocenters can be predictably controlled due to the demanding boat transition state required for the Cope rearrangement of the divinylcyclopropane intermediates. Control of the absolute stereochemistry of the process would be possible if the initial cyclopropanation was carried out in an enantioselective mode. Recently, we have reported that rhodium(II) prolinate catalysts such as **1** result in highly enantioselective intermolecular cyclopropanations (up to 95% ee)[3] and that the intermolecular reactions with dienes leads to the enantioselective synthesis of various seven-membered carbocycles (up to 90% ee).[4] In this paper, we describe that asymmetric induction can be achieved in intramolecular reactions for the synthesis of polycyclic systems. Using the rhodium(II) prolinate catalyst **1**, the potential of this process is illustrated by the asymmetric synthesis of the tremulane skeleton (**2**)[5,6] as outlined in Scheme 1.

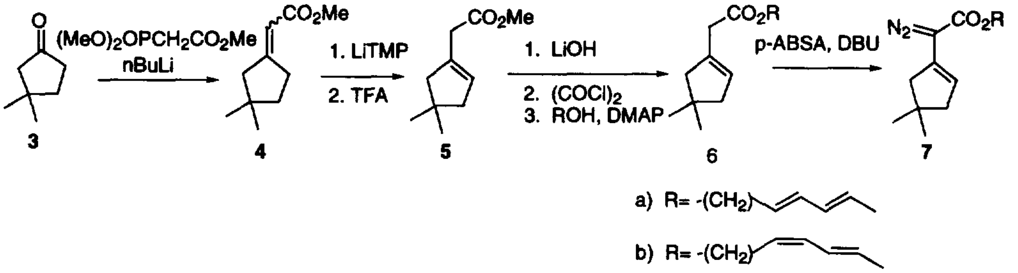
Scheme 1



Tremulane (**2**)

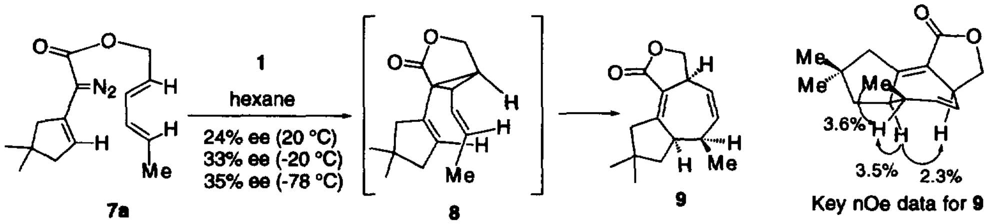
The two vinylcarbenoid precursors **7** that were used in this study were prepared as outlined in Scheme 2. The most challenging aspect of the synthesis of **7** was the control of the regiochemistry of the diazo-transfer reaction such that only the desired vinyldiazomethanes were formed. The unsaturated ester **4** was readily prepared from the cyclopentanone **3**[7] in 70% yield by a Horner-Emmons reaction but attempts at the direct diazotization of **4** proceeded in low yield and with poor regiocontrol. This problem was circumvented in the following manner. First, **4** was deconjugation by treatment with lithium tetramethylpiperidide at -94 °C followed by an acid quench to form **5** in 86% yield, contaminated with only a trace (~5%) of the other possible regioisomer. Hydrolysis of **5** with lithium hydroxide, followed by conversion to the acid chloride and treatment with the appropriate alcohol[8] gave either **6a** or **6b** in 81% overall yield. Finally, diazo-transfer on either **6a** or **6b** using p-acetamidobenzenesulfonyl azide (*p*-ABSA)[9] and DBU resulted in the formation of **7a** or **7b** in 45-55% yield.

Scheme 2



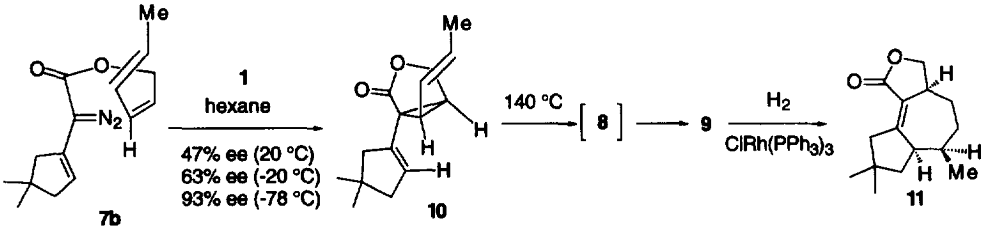
Earlier studies on intramolecular reactions between vinylcarbenoids and dienes have shown that in dienes with a *trans* double bond nearest the tether, a *cis*-divinylcyclopropane is formed which rapidly undergoes a Cope rearrangement.[10] In contrast, in dienes with a *cis* double bond nearest the tether, an isolable *trans*-divinylcyclopropane is formed. Consequently, the *trans*-diene **7a** was initially studied because it was expected to lead to the direct formation of the tremulane skeleton. Rhodium (II) (R)-prolinate (**1**)[3b] catalyzed decomposition of **7a** in hexane at room temperature resulted in the formation of the tremulane skeleton **9** in 69% yield (Scheme 3). The relative stereochemistry of **9** was determined by nOe difference analysis, and it was as expected of a reaction proceeding through the divinylcyclopropane intermediate **8**. Particularly diagnostic was the across-ring enhancement that was used to assign the relative stereochemistry at C-5 and C-8a.[11] The enantioselectivity of the reaction, however, was disappointing (24% ee).[12] Some improvement in enantioselectivity was possible by carrying out the reactions at lower temperatures (up to 35% ee at -78 °C), but still the overall results were not very satisfactory.

Scheme 3



Previous studies have shown that vinylcarbenoids do not undergo intermolecular cyclopropanations with *trans*-alkenes[13] and this has been rationalized by considering that the alkene needs to approach the rhodium-carbenoid complex in a side-on manner.[3b] Even though intramolecular reactions occur with *trans*-dienes, a possible cause for the low enantioselectivity for the reaction of **7a** may be the inability of the *trans*-diene to approach the carbenoid closely enough for the chiral influence of the catalyst to be effective. Consequently, the study was extended to the *cis*-diene **7b**. Rhodium(II) prolinate catalyzed decomposition of **7b** in hexane at room temperature resulted in the formation of the expected *trans*-divinylcyclopropane **10** in 79% yield. The *trans*-divinylcyclopropane **10** is stable under ambient conditions, but on heating in refluxing xylene, **10** underwent smooth rearrangement to the tremulane skeleton **9** in 85% yield, presumably though initial equilibration to the *cis*-divinylcyclopropane **8**. The equilibration of *cis* and *trans* divinylcyclopropanes is considered to occur via diradical intermediates.[14] The involvement of such intermediates in the equilibration between **10** and **8** would not change the chiral induction obtained during the formation of **10**, because the third stereogenic center in **10** is unaffected during the equilibration to **8**.[14] By this two step process, the overall yield of **9** was similar to that obtained from the one step process starting from the *trans*-diene **7a**. The enantioselectivity, however, of the two step process from **7b** was 47% ee, a major improvement over the result with the *trans*-diene **7a**. Further optimization of enantioselectivity in the formation **9** was obtained by carrying out the decomposition of **7b** at progressively lower temperatures (up to 93% ee at -78 °C). Completion of the synthesis of (+)-5-epi-tremulenolide **11** was readily achieved in 76% yield by hydrogenation of **9** with Wilkinson's catalyst.

Scheme 4



In summary, these studies illustrate that the tandem intramolecular cyclopropanation/Cope rearrangement is a feasible method for the synthesis of fused seven-membered carbocycles with predictable diastereoselectivity and high enantioselectivity. From these preliminary studies it appears that intramolecular cyclopropanation of *cis*-dienes is the more efficient process even though the resulting cyclopropane formed would have a *trans* arrangement of the vinyl groups. Further studies are in progress to evaluate the full scope of this chemistry and to develop a predictive model for the control of the absolute stereochemistry in these reactions.

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12. Enantiomeric excess (% ee) were determined by HPLC using a Diacel Chiralcel OJ analytical column (25 cm length, flow rate = 1.0 ml/min, 0.5% isopropanol in hexane, UV 254 nm, T_R = 13.9 min. (minor), T_R = 15.2 min (major). The studies were carried out using the rhodium(II) (R)-prolinate catalyst **1** instead of the catalyst derived from the natural amino acid in order that the minor enantiomer of the product **9** eluted first during the HPLC analysis. The depicted absolute stereochemistry of the products is based on the assumption that the carbenoid face selectivity in these reactions is the opposite to that observed in the rhodium(II) (S)-prolinate catalyzed cyclopropanations described in Ref. 3

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