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Construction of the ingenane core using an Fe(III) or Ti(IV) Lewis acid-catalyzed intramolecular [6+4] cycloaddition

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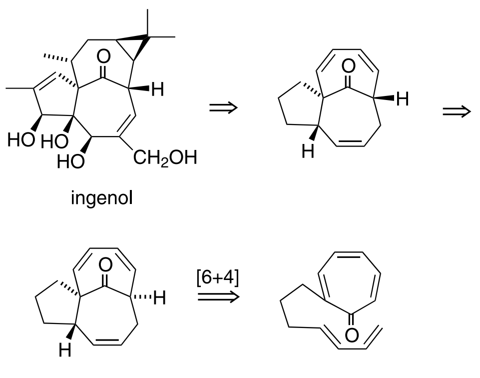
Abstract—A facile entry into the ingenane core using a Lewis acid-catalyzed intramolecular [6+4] cycloaddition has been developed. Ti(IV)- and Fe(III)-based Lewis acids were found to mediate the higher order cycloaddition in good to excellent yield at room temperature. Chiral Ti(IV) Lewis acids were found to induce modest asymmetry in the resultant [6+4] cycloadducts.

Ingenol, isolated from *E. Tirucalli* L. in 1968,[1] has been the focus of several research groups in the past few years (Scheme 1).[2] The diester of this unique diterpene is a known tumor promoter[3] and derivatives thereof boast other biological activities including protein kinase C (PKC) activation,[4] nerve growth factor (NGF) stimulation[5] and anti-HIV properties.[6] Moreover, ingenol offers several synthetic challenges including a bicyclo[4.4.1]undecene system, as well as an unusual and highly strained *trans*-intrabridgehead stereochemical relationship.[7] Recently, the Winkler group has reported the total synthesis of racemic ingenol.[2a]

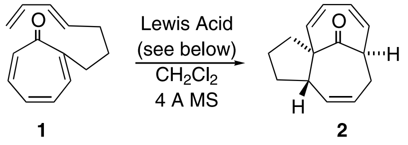
Retrosynthetic analysis shows that the ingenol skeleton can be quickly constructed using a [6+4] cycloaddition[8] in conjunction with a net isomerization of the out,out-stereoisomer into the highly strained in,out material (Scheme 1).[9] Of particular note, the entire stereochemistry of the southern perimeter of ingenol is envisioned to be derived from the *exo*-transition state of the cycloaddition event.[10]

A previous report from our laboratories disclosed the facile construction of the ingenane core using an intramolecular [6+4] cycloaddition between tropone and a pendant diene moiety (see Scheme 2).[11] Typically, these reactions proceed in good to excellent yield (> 80%), yet elevated temperatures (>80°C) were required to effect cyclization. In an effort to synthesize an optically enriched ingenane core, we realized that the symmetry allowed higher order cycloaddition would have to occur under milder conditions; therefore, we investigated the ability of a Lewis acid to promote the [6+4] cycloaddition at lower temperatures.

For years, protic acids have been known to catalyze [6+4] cycloaddition between tropone and cyclopentadiene;[12] however, until recently, Lewis acid-mediated higher-order cycloadditions were virtually unknown. An initial report by Gleason et al. revealed that $ZnCl_2$ as well as lanthanide triflates catalyze an intermolecular [6+4] cycloaddition between tropone and cyclopentadi-



Scheme 1. Retrosynthetic analysis of the diterpene ingenol.



Scheme 2.

Keywords: higher-order cycloaddition; Lewis acid; tropone; catalysis; ingenol.

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Table 1. Conditions for Lewis acid mediated intramolecular [6+4] cycloaddition of tropone **1** as shown in Scheme 2

Entry[a]	Lewis acid	Equiv.	Time (h)	Yield of **2** (%)
1	$ZnCl_2$	2.00	48	–
2	$AlEt_2Cl$	0.30	98	35
3	$BF_3{\cdot}OEt_2$	0.30	48	45–50
4	$SnCl_4$	0.30	48	55–60
5	$TiCl_4$	0.30	48	65
6	$Ti(O^iPr)_2Cl_2$	0.30	36	70
7[b]	$FeCl_3$	0.25	30	85

[a] Reactions were conducted in CH_2Cl_2 under a N_2 atmosphere in the presence of 4 Å MS.

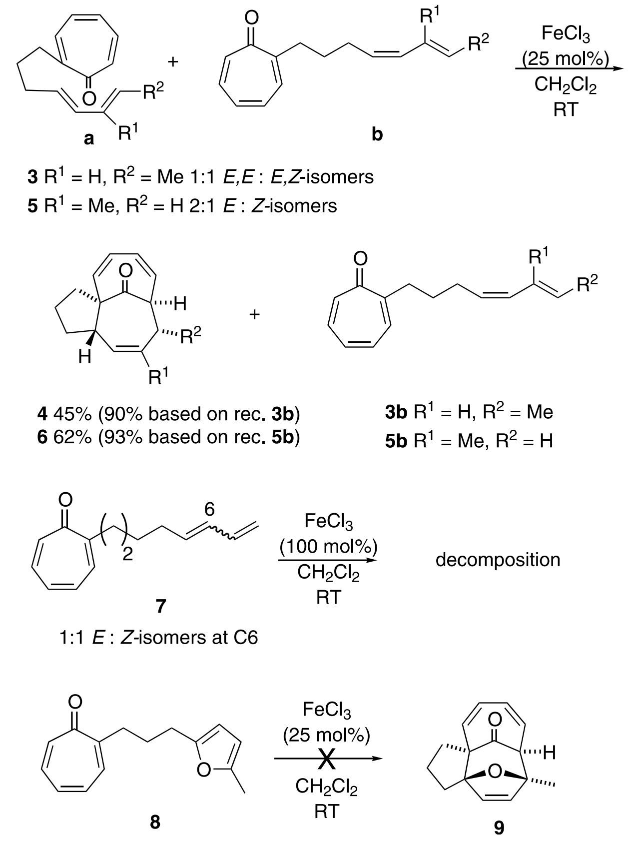
[b] Reaction was performed in the absence of 4 Å MS.

ene in good to excellent yield at room temperature.[13] Gleason's report prompted us to divulge our own results in the area of Lewis acid-catalyzed inter- and intramolecular tropone [6+4] cycloadditions.

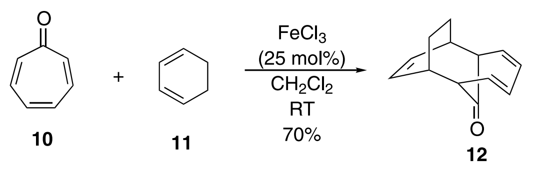
Diene substituted tropone **1**[14] was first exposed to a series of Lewis acids in CH_2Cl_2[15] in the presence of 4 Å molecular sieves (4 Å MS) at room temperature (see Table 1).[16] Treatment of **1** with $ZnCl_2$ led to no observable cyclization even after 48 h of reaction time using a stoichiometric amount of Lewis acid (entry 1). This observation was in stark contrast to what was reported by the Gleason laboratory, where $ZnCl_2$ provided [6+4] cycloadducts in good yield and short reaction times.[13] We presumed substrate **1** was less prone to cyclize than those outlined in Gleason's report,[17] and broadened our investigation to include stronger Lewis acids. During this part of the study, Ti(IV)- and Fe(III)-based Lewis acids were immediately identified as viable [6+4] catalysts (entries 5–7).

Interestingly, in the absence of 4 Å MS, the reactions catalyzed by $TiCl_4$ and $Ti(O^iPr)_2Cl_2$ led to decreased yields and significant amounts of decomposition products. The 4 Å MS may serve to remove trace amounts of water from the system to prevent destruction of the Lewis acid catalyst and eventual decomposition of the [6+4] substrate. However, 4 Å MS were not required for the $FeCl_3$ mediated cycloaddition to proceed in excellent yield (85%) at room temperature (entry 7).[18] Exposure of the [6+4] substrate **1** to 4 Å MS without any Lewis acid gave compound **2** at a rate similar to the background reaction (<10% yield after 20 days).

The conditions outlined in Table 1 were found to be tolerant of substituents on the pendant dienes (Scheme 3). A 1:1 mixture of the *E*,*E*- and *E*,*Z*-diene **3a** and **b**, respectively,[19] was exposed to 25 mol% $FeCl_3$ for 30 h at room temperature to give a 90% yield of the expected cycloadduct **4** based on recovered *E*,*Z*-isomer **3b**.[20] Likewise, the *E*-isomer of **5a** proceeded under the same conditions (30 h) to give 93% yield of **6** based on recovered *Z*-isomer **5b**. It is noteworthy that only the *E*,*E*-isomer of the pendant dienes participated in the cycloadditions, suggesting that the cycloaddition occurs via a concerted rather than stepwise process.



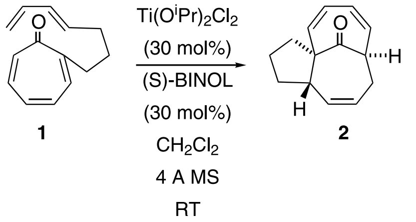
Scheme 3.



Scheme 4.

Surprisingly, substrate **7**, which bears an additional methylene group in the diene tether, proved not to undergo facile ring closure under catalytic conditions. Moreover, prolonged exposure to a stoichiometric amount of $FeCl_3$ only served to decompose compound **7**. Unfortunately, all efforts to cyclize tropone **8**[21] were unsuccessful, presumably due to the high reversibility of the furan moiety in the [6+4] cycloaddition.[22]

The Fe(III) catalyst was also found to mediate an intermolecular [6+4] cycloaddition. Treatment of tropone **10** and 1,3-cyclohexadiene **11** with 25 mol% $FeCl_3$ for 36 h lead to cycloadduct **12** in 70% yield (Scheme 4).[23] It is noteworthy that no [4+2] side products were observed in this reaction. Other Lewis acids (e.g. $TiCl_4$, $Ti(O^iPr)_2Cl_2$, $SnCl_4$, etc.) failed to promote cyclization even when used in stoichiometric amounts. When iron chloride was used to promote an intermolecular [6+4] cycloaddition between tropone and acyclic dienes (e.g. isoprene, 2,3-dimethylbutadiene, etc.) only trace amounts of the desired cycloadducts were isolated. Apparently, the *cis*-locked conformation of the cyclic diene greatly enhances the rate in which the [6+4] cycloaddition occurs.



Scheme 5.

Encouraged by these results, we decided to screen a chiral Lewis acid in an effort to produce an optically enriched ingenane core. Exposure of **1** to Ti(IV)–(*S*)-BINOL[24] complex for 36 h at room temperature produced cycloadduct **2** in 80% yield and 40% ee[25] (Scheme 5). Currently, work is under way to improve upon these promising results.

In conclusion, we have identified conditions that initiate an inter- or intramolecular [6+4] cycloaddition at room temperature. Our conditions allow unactivated tropone and diene substrates to undergo facile ring closure and nicely compliment the findings outlined by the Gleason group.[13] We are currently investigating methods to improve catalyst loading, reaction rate and enantioselectivity with chiral Lewis acids. Studies on this aspect of [6+4] cycloaddition chemistry will be reported in due course.

Acknowledgements

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14. Substrate **1** was generated from the Grignard reagent derived from 7-bromoheptadiene and chlorotropone. For a general procedure on the synthesis of compound **1** see Ref. 11.
15. Reactions carried out in toluene or benzene led to decomposition of the starting material, even in the presence of 4 Å MS. Two equivalents of BF_3·OEt_2 in Et_2O led to **2** in 61% yield after 120 h of reaction time.
16. **General procedure for Lewis acid-catalyzed intramolecular [6+4] cycloaddition**: A solution of [6+4] substrate **1** (0.2 mmol) and 4 Å MS (100 mg, if necessary) in CH_2Cl_2 (2 mL) was charged with a Lewis acid (25–30 mol%) at room temperature. The reaction was allowed to stir at this temperature until starting material was consumed as monitored by thin-layer chromatography (TLC). Upon completion, the reaction was placed directly on a silica gel column and eluted with 3:1 hexanes/EtOAc to give the desired [6+4] cycloadduct.
17. Gleason reports that the [6+4] cycloaddition between 2-siloxybutadiene and a variety of electron deficient tropones occurs efficiently at room temperature in the absence of $ZnCl_2$ within 24 h and instantaneously with the Lewis acid at the same temperature. It is likely that the presence of the strong electron donating substituent on the diene or electron withdrawing groups on the tropone serve to activate the system for facile [6+4] cycloaddition (see Ref. 13).
18. Exposure of substrate **1** to $FeCl_3$ with 4 Å MS produced compound **2** in comparable yield (80%).
19. The diene side-chains of structures **3**, **5** and **7** were prepared via Wittig chemistry with semistabilized allylphosphonium ylides. For a procedure see Ref. 11.
20. The diene geometry for compounds **3**, **5** and **7** were deduced from ^{1}H NMR coupling constants.
21. Compound **8** was synthesized via a Grignard addition between 3-(2-methylfuranyl)-propylmagnesium chloride

and 2-chlorotropone in 78% yield (for a detailed experimental procedure, see: Rege, S. D. Ph.D. Dissertation, Wayne State University, 1988).

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