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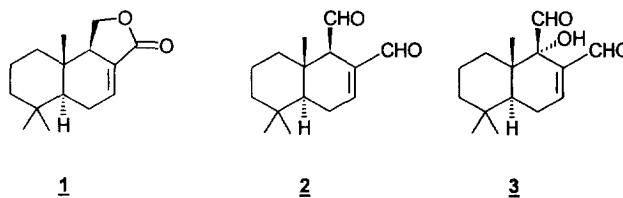
High Pressure Diels Alder Reactions of 1-Vinyl-2,2,6-trimethylcyclohexene Catalyzed by Chiral Lewis Acids; An Enantioselective Route to a Drimane Sesquiterpene Precursor.

Joop Knol, Auke Meetsma and Ben L. Feringa*

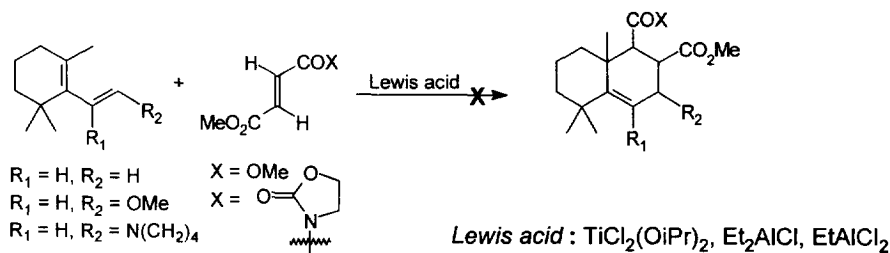
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Abstract: The Diels Alder reaction of 1-vinyl-2,2,6-trimethylcyclohexene **4** and 3-((E)-3-(methoxycarbonyl)propenyl)-1,3-oxazolidin-2-one **5** under high pressure, catalyzed by a chiral bis-imine copper(II) complex, yields a drimane sesquiterpene precursor in a highly regio- and diastereoselective manner with enantioselectivities up to 64%; nearly enantiomerically pure material is obtained by one simple crystallization.

Drimane sesquiterpenes like drimenin, cinnamolide **1**, polygodial **2** and warburganal **3** are naturally occurring compounds with a broad spectrum of biological activities such as insect antifeedant¹ and cytotoxic properties.



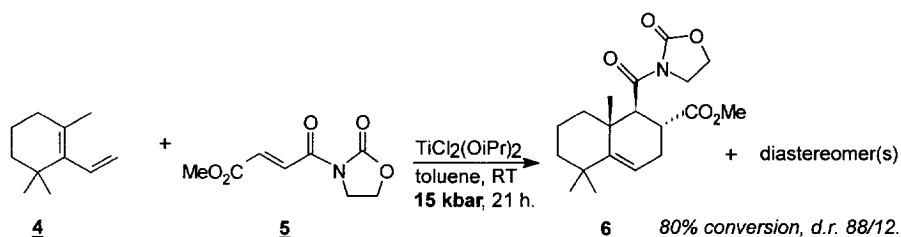
The need for enantiomerically pure drimanes² is emphasized by the fact that certain racemic drimanes are too cytotoxic for pharmaceutical applications. Amongst the reported total syntheses of drimanes, very few have led to optically active products unless the starting material is obtained from the chiral pool.³ Synthetic



Scheme 1.

strategies based on (thermal) Diels Alder reactions of 1-vinyl-2,2,6-trimethylcyclohexene derivatives with either acetylenic⁴ or olefinic⁵ dienophiles have also been described. On the basis of these reports we have extensively studied the reactions of different combinations of dienes, (chiral) dienophiles⁶ and Lewis acid catalysts, including the use of chiral Lewis acids.⁷

Unfortunately these reactions resulted in low conversions, frequently accompanied by decomposition of the reactants as the major pathway (scheme 1). To overcome these problems, the combined use of high pressure and a mild Lewis acid catalyst was investigated.⁸ The high pressure (15 kbar) Diels Alder reaction of 3-((E)-3-(methoxycarbonyl)propenoyl)-1,3-oxazolidin-2-one **5**⁹ with excess 1-vinyl-2,2,6-trimethylcyclohexene **4**, catalyzed by $\text{TiCl}_2(\text{OiPr})_2$ (20 mol%) gave 80% conversion after 21 hours at room temperature (scheme 2).



Scheme 2.

¹H-NMR analysis of the reaction mixture after removal of the catalyst showed the clean formation of the Diels Alder product **6** together with minor amounts of other diastereomeric products^{10,11} (d.r. 88/12). After chromatographic purification (SiO_2 , ether/hexane 6/4) a single diastereomeric product was obtained.¹² ¹H-NMR spectroscopy indicated the relative stereochemistry shown in **6** but unequivocal structural proof was based on X-Ray crystallographic analysis¹³ (figure 1) which clearly shows the relative $\text{C}_9\beta$ stereochemistry.¹⁴ As a logical extension, modified alkoxytitaniumdichlorides, derived from chiral diols, were investigated as chiral Lewis acid catalysts. Experiments with the chiral Lewis acids **7a** and **7b** showed no significant levels of asymmetric induction after relatively prolonged reaction times (44 h.) (table). The notion that more active Lewis acid catalysts were needed in this reaction turned our attention towards the use of chiral cationic copper(II)bis-imine complexes.¹⁵ Indeed a significant improvement was observed with catalyst **8** derived from copper(II)triflate and (1*R*,2*R*)-*N,N'*-bis-(2,6-dichlorobenzylidene)-diaminocyclohexane.^{16,17} With this catalyst, high conversions (91-100%) and good diastereoselectivities (up to 93/7) were observed after 16 hours at room temperature. Even with nearly stoichiometric amounts of diene (1.1-1.5 eq.) smooth cycloaddition was found. From control experiments (see table) a non enantioselective contribution of the uncatalyzed reaction during chiral catalysis was expected to be present at 15 kbar (entry 3-6). Although the uncatalyzed reaction could be nearly fully suppressed by lowering the pressure to 12 kbar (entry 7,8), no significant change in enantioselectivity (e.e. 60-64%) was observed.¹⁸ This indicates the optimal selectivity of this reaction with the

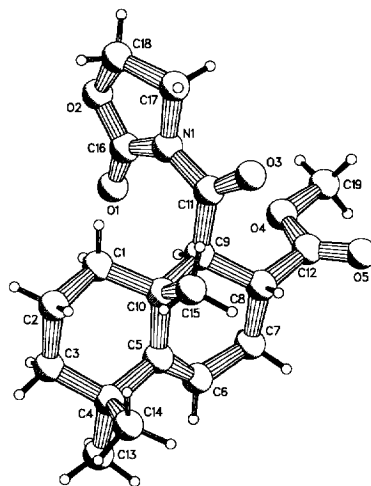
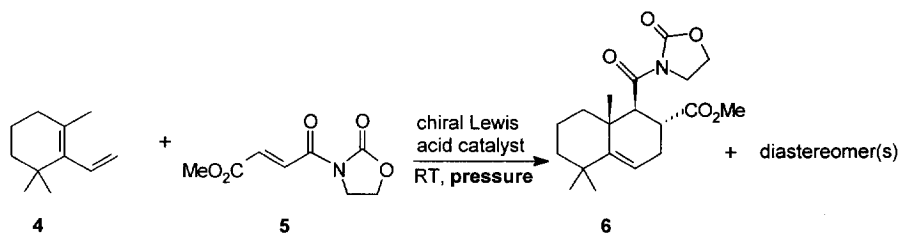


figure 1. Pluto drawing of **6** with adopted numbering scheme.

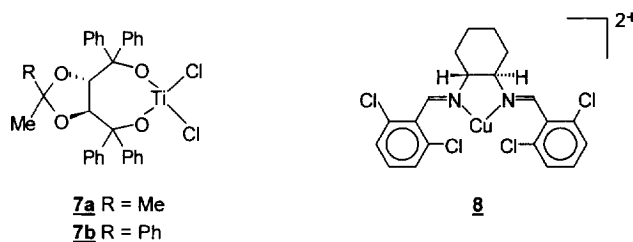
present catalyst and the conditions used.

Table.



entry ^a	Chiral Lewis Acid	equiv. diene	pressure (kbar)	conversion ^{b,c} (%)	diastereomeric ratio ^b	yield ^d (%)	e.e. ^e (%)
1	<u>7a</u>	4	15	82(n.d.)	n.d.	30	6
2	<u>7b</u>	4	15	33(n.d.)	n.d.	66	0
3	<u>8</u>	4	15	100(n.d.)	89/11	55	43
4	<u>8</u>	2	15	100(47)	93/7	74	61
5	<u>8</u>	1.5	15	98(30)	92/8	68	61
6	<u>8</u>	1.1	15	91(23)	88/12	66	64
7	<u>8</u>	4	12	92(14)	88/12	67	63
8	<u>8</u>	2	12	98(8)	91/9	65	60

a) Catalytic reactions were performed in the presence of 20 mol% catalyst in either toluene (entry 1,2) or dichloromethane (entry 3-8) as a solvent. b) determined by ¹H-NMR analysis of the crude reaction mixtures. c) numbers in brackets represent conversions of independently performed reactions in the absence of catalyst. d) isolated yields after chromatographic purification. e) determined by ¹H-NMR after addition of 0.7 eq. Eu(hfc)₃.



Although complete stereocontrol was not observed in our catalytic reactions, nearly enantiomerically pure **6** could be obtained (e.e. 94%) by one crystallization from a *t*-butyl methyl ether/petroleum ether mixture.¹⁹

In summary we have demonstrated the catalytic enantioselective synthesis of a potential drimane sesquiterpene precursor and the successful use of chiral Lewis acid catalysis in a high pressure Diels Alder reaction resulting in significant asymmetric induction. Optimization studies with respect to enantioselectivity and elucidation of the absolute stereochemistry of **6** are under current investigation.

Acknowledgements

Dr. J.W. Scheeren and Drs. J.P.G. Seerden (University of Nijmegen) are greatly acknowledged for the use of high pressure equipment and practical assistance. This research was financially supported by the Innovation Oriented Research Program (IOP) on Catalysis (no. 90031) of the Dutch Ministry of Economic Affairs.

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11. Minor amounts of diastereomeric products were easily detected in the methoxy region of the 200 MHz ¹H-NMR spectrum of the crude product. No attempts were made to isolate or elucidate the structures of these diastereomers.
12. Selected data of **6**: ¹H NMR (300 MHz, CDCl₃): δ 1.07 (s, 3H), 1.12 (s, 3H), 1.23 (s, 3H), 1.38 (m, 4H), 1.72 (m, 2H), 2.20 (ddd, J = 18.1, 11.8, 3.1 Hz, 1H), 2.51 (ddd, J = 18.1, 7.1, 4.6 Hz, 1H), 3.24 (ddd, J = 11.8, 11.8, 7.1 Hz, 1H), 3.63 (s, 3H), 4.02 (m, 2H), 4.32 (d, J = 11.8 Hz, 1H), 4.36 (m, 2H), 5.45 (dd, J = 4.6, 3.1 Hz, 1H); ¹³C NMR (75.43 MHz, CDCl₃): δ 17.93, 22.48, 29.02, 30.80, 32.48, 35.46, 36.85, 38.74, 39.33, 40.25, 42.97, 49.35, 51.73, 61.21, 116.55, 149.76, 153.38, 175.47, 175.73; Anal. calcd. for C₁₀H₂₇NO₅: C, 65.31; H, 7.79; N, 4.01. Found C, 65.19; H, 7.75; N, 3.86.
13. Crystal data for **6**: C₁₀H₂₇NO₅, *M_r* = 349.43, orthorhombic, spacegroup *Pbca*, *a* = 12.902(1), *b* = 12.824(1), *c* = 21.501(1) Å, *V* = 3557.5(4) Å³, *Z* = 8, *D_x* = 1.305 g cm⁻³, λ(Mo Kα) = 0.71073 Å, μ = 0.88 cm⁻¹, *F*(000) = 1504, *T* = 130 K, *R_F* = 0.047 for 2071 unique observed reflections with *I* ≥ 2.5 σ(*I*) and 334 parameters.
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18. The somewhat diminished enantioselectivities observed with catalyst **8** under high pressure, compared with those reported at ambient pressure, implies a small change in transition state geometry.
19. Recrystallization of a scalemic sample (e.e. 62%) afforded crystalline material with lower e.e. (~20%) and enriched mother liquor (e.e. 94%).

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