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# Synthesis and Characterization of In-Plane and Out-of-Plane Enone−Lewis Acid Complexes: Implications for Diels−Alder Reactions[1]

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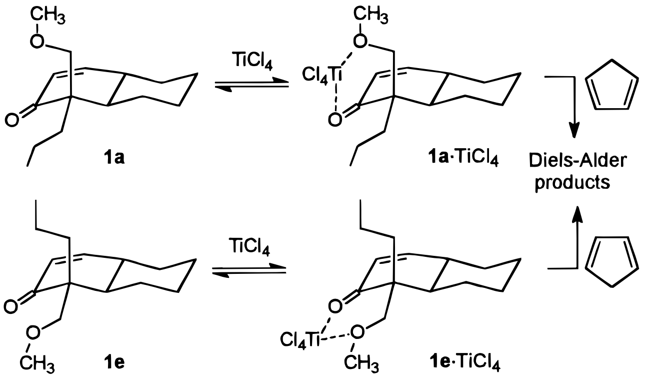
In order to determine the *reactive* geometries of enone−TiCl$_4$ complexes in Diels−Alder reactions compounds **1a**·TiCl$_4$ and **1b**·TiCl$_4$ were prepared. A crystal structure of **1a**·TiCl$_4$ confirmed that the titanium in this complex has the desired out-of-plane geometry, with a Ti−O═C−C dihedral angle of 57.6°, a value remarkably similar to dihedral angles found in simple carbocyclic compounds. Difference NOE studies support a similar geometry in solution. The magnitudes of key $^1$H and $^{13}$C NMR chemical shift changes upon complex formation indicate that the out-of-plane TiCl$_4$ in **1a**·TiCl$_4$ is a stronger Lewis acid than the in-plane TiCl$_4$ of **1e**·TiCl$_4$. These results are further supported by the changes in carbonyl stretching frequencies upon complex formation, with a $\Delta\nu_{C=O}$ for **1a**·TiCl$_4$ which is 24 cm$^{-1}$ larger than that for **1e**·TiCl$_4$. Expectations of heightened reactivity for **1a**·TiCl$_4$ as compared to **1e**·TiCl$_4$ have been confirmed; the former complex undergoes Diels−Alder reactions with cyclopentadiene 15 times more rapidly than the latter, despite being disfavored on a thermodynamic basis. These results suggest that the commonly held assumption of an in-plane reactive geometry for titanium-based Lewis acid-mediated Diels−Alder reactions may be in error.

Though differing in the details of the chiral scaffolding, the designs of chiral Lewis acids for the conversion of achiral diene/dienophile combinations into optically pure Diels−Alder cycloaddition products have been predicated on the assumption of a coordination geometry in which the Lewis acidic atom is in the plane of the carbonyl group.[2] The underlying basis for this critical assumption is the known thermodynamic preference for such a geometry in complexes involving electron deficient Lewis acids,[3] as indicated by spectroscopic, crystallographic, and computational studies;[4] however, the *reactive* geometry of a molecule or complex is not necessarily identical to the thermodynamically preferred geometry.[5,6]

The axial and equatorial methoxymethyl groups of compounds **1a** and **1e** were designed to direct coordination of TiCl$_4$ to out-of-plane and in-plane geometries, respectively.[7] We found that although there is indeed a thermodynamic preference for the in-plane coordination geometry of **1e**·TiCl$_4$ (~6:1), it was the presumed out-of-plane complex **1a**·TiCl$_4$ which was the more reactive in Diels−Alder reactions with cyclopentadiene ($k_{rel}$ = 15). While these results cast doubt on the commonly held assumption of in-plane reactive geometries in Lewis acid catalyzed Diels−Alder reactions, they are compelling only to the extent to which one may assume that the complex **1a**·TiCl$_4$ has the coordination geometry which we intended.[8] We report here that there is strong evidence for an out-of-plane coordination geometry in **1a**·TiCl$_4$ in both solution and the solid state. Furthermore, the magnitudes of the spectral shifts attendant on formation of the complexes **1e**·TiCl$_4$ and **1a**·TiCl$_4$ lead to an expectation of the greater reactivity of the latter.



Our original synthetic route to compounds **1a** and **1e** suffered from two flaws: a low yielding sequence involving a Robinson annulation to construct the bicylco[4.4.0] framework of the targets, and more seriously, an undesirably *high* degree of diastereoselectivity in the introduction of the methoxymethyl groups, ultimately leading to a 6:1 preference for the production of **1a** over **1e**. In order to circumvent the Robinson annulation we hoped to make use of a sequence involving alkylation of the anion derived from the Birch reduction product of an appropriate alkoxy tetrahydronaphthalene.[9] To this end, 2-methoxy-5,6,7,8-tetrahydronaphthalene was reduced to

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[1] Portions of this work were presented at the 34th National Organic Symposium, June, 1995, Williamsburg, VA.

[2] Two recent related studies of chiral Lewis acids which also provide leading references to the literature in this field: (a) Haase, C.; Sarko, C. R.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 1777. (b) Seebach, D.; Dahinden, R.; Marti, R. E.; Beck, A. K.; Plattner, D. A.; Kühnle, F. N. M. *J. Org. Chem.* **1995**, *60*, 1788.

[3] As a consequence of M → C back bonding, formation of out-of-plane ($\eta^2$- and $\eta^4$-) complexes of saturated and unsaturated carbonyl compounds with electron rich transition metals is not unusual: for leading references, see ref 8.

[4] The literature is extensive. The recent work by Denmark and Almstead is particularly detailed and includes a discussion of this issue which constitutes a review for all practical purposes: Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1993**, *115*, 3133.

[5] Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

[6] Ironically, a particularly apt example of this may be found in the extensive and detailed studies of Gladysz and co-workers on $\pi$-complexes of carbonyls with chiral rhenium compounds, in which nucleophilic addition to the carbonyls was found to occur by way of a small concentration of highly reactive in-plane complex. For leading references, see (a) Wang, Y.; Gladysz, J. A. *J. Org. Chem.* **1995**, *60*, 903. (b) Klein, D. P.; Gladysz, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 8710.

[7] Corcoran, R. C.; Ma, J. *J. Am. Chem. Soc.* **1991**, *113*, 8973.

[8] Corcoran, R. C.; Ma, J. *J. Am. Chem. Soc.* **1992**, *114*, 4536.

[9] Rabideau, P. W.; Marcinow, Z. *Org. React.* **1992**, *42*, 1.

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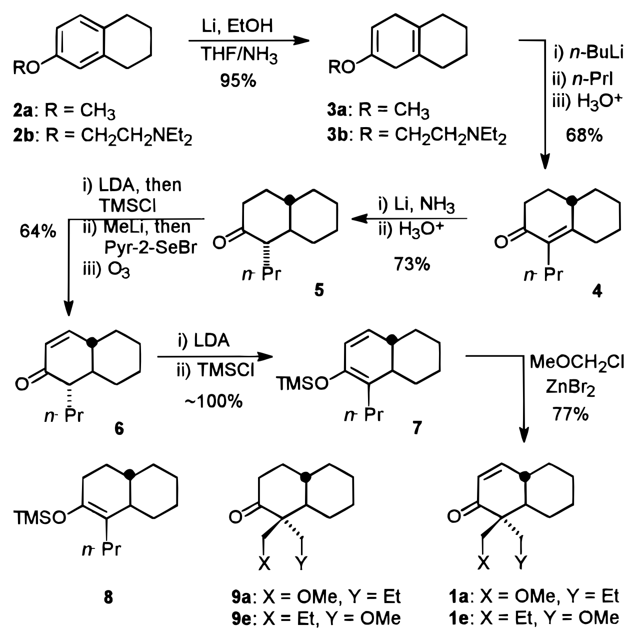
**Scheme 1. Synthesis of 1a and 1e**



the known nonconjugated dienol ether **3a** in >90% yield[10] (Scheme 1). We were unable to achieve satisfactory results in the deprotonation and alkylation of **3a**, even using n-BuLi/HMPA/THF, or n-BuLi/t-BuOK at temperatures from −78 °C to ambient. As a consequence, we took advantage of the methodology of Sutherland and co-workers,[11] who had experienced difficulties in analogous metalations. Alkylation of 5,6,7,8-tetrahydro-2-naphthol with *N*,*N*-diethyl-2-chloroethylamine gave ether **2b** (97% yield) which was then reduced to the dienol ether **3b** in 95% yield. This compound was smoothly deprotonated at −78 °C and alkylated with iodopropane, and the crude product was directly hydrolyzed to give the previously synthesized hexahydro-1-propyl-2-naphthalenone **4** in 68% yield (63% from 5,6,7,8-tetrahydro-2-naphthol), along with 5−7% of what appears (by $^1$H NMR) to be the isomeric 3-propyl enone.

In our original route, reductive generation of enol silane **8** from **4** was followed by methoxymethylation with chloromethyl methyl ether to give a 6:1 mixture of octahydronaphthalenones **9a** and **9e**. We reasoned that the stereoelectronic preference for the axial methoxymethylation could be lowered by performing the reaction on a more nearly flat dienol silane substrate **7**. To this end, the double bond in enone **4** was transposed by the route shown to give the isomeric **6** in 47% overall yield. Conversion to the dienol silane **7** was followed by methoxymethylation with chloromethyl methyl ether. As had been hoped, the diastereoselectivity of this reaction was substantially lower than had been observed for the reaction of **8**, producing a 3.5:1 ratio of **1a** to **1e**.

Crystals of **1a**·$TiCl_4$ were obtained by deposition of hexane on a methylene chloride solution of the complex.[12,13] The X-ray crystal structure of **1a**·$TiCl_4$ clearly shows an out-of-plane coordination geometry, as had been intended (Figures 1 and 2, Tables 1−3). In a quantitative sense this out-of-plane geometry is indicated by the 57.6° Ti−O(1)−C(3)−C(4) dihedral bond angle (Table 1). Difference NOE experiments strongly support a solution structure for **1a**·$TiCl_4$ which is similar to that seen in the solid state. Irradiation of the more downfield of the two diastereotopic methylene protons of the methoxymethyl group of **1a** results in a 5.4% enhancement of the allylic bridgehead proton intensity, confirming the axial orientation of this group. A similar experiment with **1a**·$TiCl_4$ gives a 2.9% enhancement,[14] also indicating an axial orientation of the methoxymethyl group.

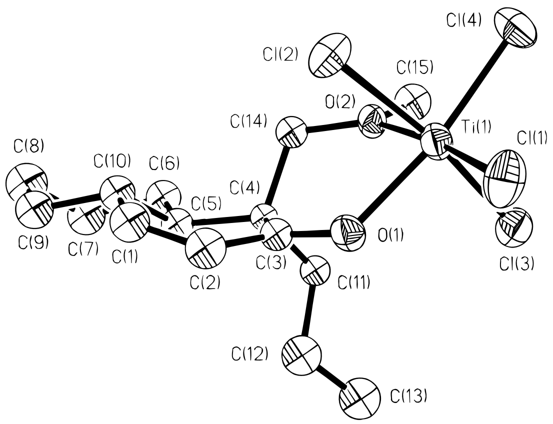


**Figure 1.** ORTEP of **1a**·$TiCl_4$. Hydrogens are omitted for clarity.

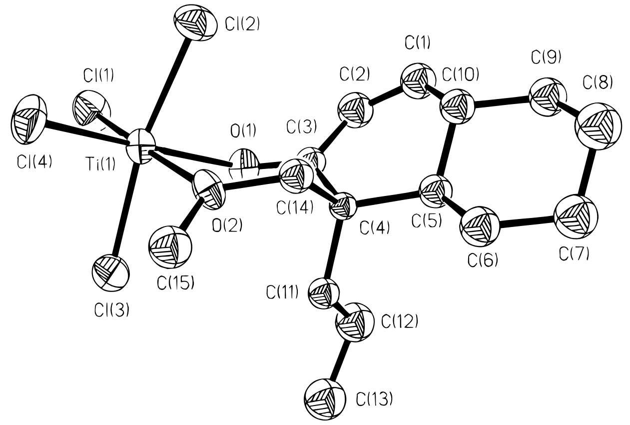
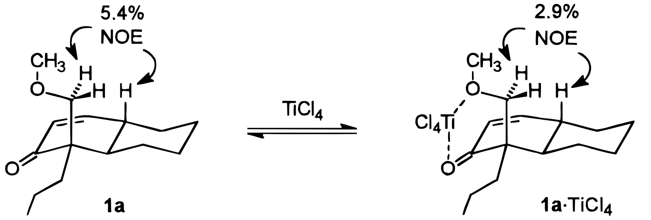


**Figure 2.** ORTEP of **1a**·$TiCl_4$. Hydrogens atoms are omitted for clarity.



Differences in the magnitudes of $^1$H and $^{13}$C NMR chemical shift changes of **1a** and **1e** upon complex formation are indicative of different solution state structures (Table 4). Of particular note in the $^1$H NMR

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[10] Wilds, A. L.; Nelson, N. A. *J. Am. Chem. Soc.* **1953**, *75*, 5360.

[11] Amupitan, J.; Hug, E.,; Mellor, M.; Scovell, E. G.; Sutherland, J. K. *J. Chem. Soc., Perkin Trans. 1* **1983**, 747.

[12] Attempts to obtain crystals of **1e**·$TiCl_4$ have been unsuccessful.

[13] Compound **1a**·$TiCl_4$ crystallizes in the monoclinic space group $P2_1/n$, with $a = 7.423(2)$ Å, $b = 15.111(3)$ Å, and $c = 17.209(3)$ Å, $\beta = 96.72(3)°$, $V = 1916.9(7)$ Å$^3$, and density$_{calc}$ = 1.476 g cm$^{-3}$. The structure was solved and refined by full-matrix least-squares methods to conventional $R$ factor values of $R_{obs} = 0.0609$ and $wR_{obs} = 0.0665$ using 847 observed reflections with $I > 3\sigma(I)$ collected at 23 °C using Mo Kα ($\lambda = 0.71073$ Å) radiation with $4° < 2\theta < 45.0°$. The X-ray data has been submitted to the Cambridge Crystallographic Data Centre.

[14] Control experiments with **1e** and **1e**·$TiCl_4$ showed no enhancements, as expected.

**Table 1. Selected Dihedral Bond Angles in 1a·TiCl$_4$**

| entry | atoms defining dihedral angle | dihedral angle, deg | entry | atoms defining dihedral angle | dihedral angle, deg |
|---|---|---|---|---|---|
| 1 | Ti−O(1)−C(3)−C(4) | 57.6 | 7 | O(1)−C(3)−C(4)−C(11) | 54.5 |
| 2 | Ti−O(1)−C(3)−C(2) | −117.6 | 8 | O(1)−C(3)−C(2)−C(1) | 156.6 |
| 3 | Ti−O(2)−C(14)−C(4) | −56.0 | 9 | C(3)−C(2)−C(1)−C(10) | 9.5 |
| 4 | O(2)−Ti−O(1)−C(3) | −33.4 | 10 | C(3)−C(4)−C(14)−O(2) | 59.4 |
| 5 | O(1)−Ti−O(2)−C(14) | 34.1 | 11 | C(5)−C(6)−C(7)−C(8) | 56.1 |
| 6 | O(1)−C(3)−C(4)−C(14) | −61.9 | 12 | C(6)−C(7)−C(8)−C(9) | −56.1 |

**Table 2. Selected Bond Lengths for 1a·TiCl$_4$**

| entry | bond | bond length, Å | entry | bond | bond length, Å |
|---|---|---|---|---|---|
| 1 | Ti−O(1) | 2.024(10) | 6 | Ti−O(2) | 2.184(9) |
| 2 | Ti−Cl(1) | 2.224(5) | 7 | Ti−Cl(2) | 2.319(5) |
| 3 | Ti−Cl(3) | 2.290(6) | 8 | Ti−Cl(4) | 2.244(5) |
| 4 | O(1)−C(3) | 1.246(18) | 9 | O(2)−C(15) | 1.451(19) |
| 5 | C(1)−C(2) | 1.330(23) | 10 | C(2)−C(3) | 1.444(24) |

**Table 3. Selected Bond Angles for 1a·TiCl$_4$**

| atoms | bond angle, deg | atoms | bond angle, deg |
|---|---|---|---|
| Ti−O(1)−C(3) | 132.1 (9) | O(1)−Ti−O(2) | 79.7 (4) |
| O(1)−Ti−Cl(1) | 94.2 (3) | Ti−O(2)−C(15) | 121.7 (8) |
| O(1)−Ti−Cl(2) | 83.7 (3) | C(14)−O(2)−C(15) | 112.3 (10) |
| O(1)−Ti−Cl(3) | 88.7 (3) | O(1)−C(3)−C(4) | 121.1 (14) |
| O(1)−Ti−Cl(4) | 167.9 (3) | C(1)−C(2)−C(3) | 120.0 (15) |

**Table 4. Spectral Changes upon Complex Formation with TiCl$_4$**

| spectral feature | **1a** | **1a**·TiCl$_4$ | overall change | **1e** | **1e**·TiCl$_4$ | overall change |
|---|---|---|---|---|---|---|
| $^1$H NMR, ppm | | | | | | |
| $\beta$-C=C*H* | 6.60 | 7.41 | 0.81 | 6.56 | 7.28 | 0.72 |
| CH$_2$OC*H*$_3$ | 3.18 | 3.90 | 0.72 | 3.25 | 4.16 | 0.91 |
| C*H*$_2$OCH$_3$ | 3.43 | 4.62 | 1.19 | 3.88 | 4.82 | 0.94 |
| | 3.31 | 3.58 | 0.27 | 3.17 | 3.89 | 0.72 |
| $^{13}$C NMR, ppm | | | | | | |
| *C*=O | 202.7 | 219.1 | 16.4 | 202.0 | 215.2 | 13.2 |
| $\beta$-C=*C* | 154.6 | 170.5 | 15.9 | 153.6 | 168.4 | 14.8 |
| CH$_2$O*C*H$_3$ | 59.4 | 68.6 | 9.2 | 59.3 | 71.1 | 11.8 |
| IR, $\nu_{C=O}$, cm$^{-1}$ | | | | | | |
| | 1675 | 1572 | −103 | 1674 | 1595 | −79 |

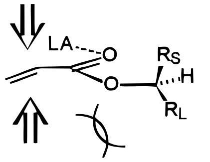
[a] Shift data for $^1$H obtained from room temperature solutions 0.020 M in substrate and TiCl$_4$ in CD$_2$Cl$_2$. $^{13}$C NMR and IR spectra were obtained analagously from 0.10 M solutions.

spectrum, $\Delta\delta$ for the $\beta$-enone proton of **1a** is almost 0.1 ppm greater in magnitude than that for **1e**.[15] In the $^{13}$C NMR the $\Delta\delta$ values for the carbonyl and $\beta$-enone carbons of **1a** are 3.2 and 1.1 ppm greater in magnitude than the corresponding values for **1e**. The most striking difference in the spectra of the two series are the magnitudes of the change in the infrared C=O stretching frequencies upon complex formation, with a $\Delta\nu_{C=O}$ of −103 cm$^{-1}$ for **1a**/**1a**·TiCl$_4$ and −79 cm$^{-1}$ for **1e**/**1e**·TiCl$_4$.

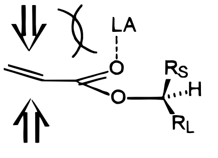
## Discussion

Stereoselectivities in Lewis acid mediated Diels−Alder reactions have been explained on the basis of a model which assumes cycloaddition to an *s-trans* enone. This geometry is thought to be the consequence of a (presumed) in-plane coordination of the Lewis acid (LA) in an E$_{C=O}$-relationship with respect to Y in C=C−C(Y)=O---LA which disfavors the *s-cis* conformer due to steric hindrance between the Lewis acid and the olefin. This model has been strongly supported through calculations by Houk and co-workers.[16] When cautiously applied this model is flexible in the sense that it allows for the possibility of *s-cis* enone geometries in special circumstances (e.g., tertiary amides[2]), and we have no reason to doubt the generality of the model *for the boron-derived Lewis acids which served as the basis for Houk's calculations*. However, application of this model to systems involving other Lewis acids appears to be fraught with risk, since the assumption of an in-plane coordination geometry may be incorrect.[17]

Any challenge to the assumption of in-plane reactive geometries in Lewis acid-mediated Diels−Alder reactions must address three issues: (1) whether out-of-plane reactive geometries can explain previously observed stereochemical results, (2) whether out-of-plane coordination geometries are thermodynamically accessible, and (3) whether coordination in an out-of-plane geometry may be expected to result in a sufficiently large increase in reactivity to compensate for a (generally) lower concentration. With regard to the first of these issues, *the assumption of an out-of-plane coordination geometry will often lead to the same predictions of diastereofacial selectivities as those derived from the assumption of an in-plane geometry.* Removal of the Lewis acid from the plane of the carbonyl should also remove, or at least strongly attenuate, any steric bias against the preferred *s-cis* enone geometry.[16a,18] Out-of-plane coordination of a Lewis acid to a chiral ester, for example, is expected to occur distal to the larger R$_L$, and subsequent cycloaddition should take place *anti* to the proximate Lewis acid. The resultant stereochemistry of this addition is the same as that predicted by the "classical" model described above.[19]



*s*-trans enone, in-plane complex
**prediction:** *re* addition



*s*-cis enone, out-of-plane complex
**prediction:** *re* addition

The assumption of a thermodynamic *preference* for in-plane coordination geometries in complexes of enones with electron deficient Lewis acids appears to be on firm

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(15) $\Delta\delta = \delta$(substrate·TiCl$_4$) − $\delta$(substrate).

(16) (a) Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14. (b) Pascual-Teresa, B.; Gonzalez, J.; Asensio, A.; Houk, K. N. *J. Am. Chem. Soc.* **1995**, *117*, 4347.

(17) A recently published crystal structure of a dienophile−(Ti-TADDOL) complex (Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1995**, *117*, 4435) differs substantially from that expected from transition state models proposed by the authors of ref 2 and by Corey and Matsumura (Corey, E. J.; Matsumura, Y. *Tetrahedron Lett.* **1991**, *32*, 6289). Only in DiMare's work (ref 2a) was a structure somewhat similar to that found in the crystal structure considered, but this was rejected due (in part) to the lack of obvious facial bias to diene approach to the assumed *in-plane complex* of the dienophile. The crystal structure reveals an *out-of-plane* coordination geometry, and a dienophile facial bias is clearly evident.

experimental and theoretical[20] footings. However, while spectroscopic studies are stongly supportive of in-plane coordination geometries, we[8] and others[4] have pointed out that the sensitivities and time scales of these techniques make it difficult to exclude the possibility of small concentrations of isomeric complexes. There is a growing body of crystallographic evidence that out-of-plane coordination geometries are thermodynamically accessible in the case of titanium-based Lewis acids. In a search of the Cambridge Crystallographic Database for the fragment Ti−O═C, 17% of the structures found (11 of 65) had Ti−O═C−Y dihedral angles of greater than 45°;[21] this fraction increases to almost one-fourth when one considers dihedral angles of greater than 30°.[22] Examination of the structures of these out-of-plane complexes does not reveal an unambiguous method by which this geometry might be predicted. It does *not* seem that chelation is a particularly important determinant; while out-of-plane complexes involving six-,[21f,22c] seven-,[21e,f,h] and eight-membered[21b] ring chelates of the titanium exist, so do nonchelated complexes.[21a,c,d,g−i,22a,b] All but one[22b] of the complexes cited involve carbonyls which are electron rich either by virtue of conjugation to a double bond[21b,e,22a,c] or aromatic ring,[21a,c,d,g,i] and/or by attachment to a heteroatom such as oxygen[21a,c−i] or nitrogen.[21b,22c] This trend may indicate a lesser thermodynamic preference for in-plane coordination geometries in the case of electron rich carbonyls and is in accord with our observations on the relative stabilities of in-plane and out-of-plane $TiCl_4$ complexes of structurally related enones and their saturated ketone Diels−Alder products.[7] A particularly interesting trend may be seen by examination of those complexes in which there are two or more different carbonyl oxygens coordinated to the titanium; in 10 of 11 cases (including **1a**·$TiCl_4$), the shorter of the oxygen−titanium bond lengths is to the carbonyl to which titanium is bound in a *more* out-of-plane geometry.[23] While it may be tempting to ascribe this trend to a less sterically hindered approach of the Lewis acid to the carbonyl oxygen,[19] examination of these out-of-plane complexes in conjunction with similar in-plane complexes does not always reveal an obvious steric bias in the case of the former.

In spite of these large numbers of exceptions to the “rule” that in-plane coordination geometries will result from the complexation of an electron deficient Lewis acid with a carbonyl oxygen, it might be argued that these examples of out-of-plane complexes are simply a consequence of packing forces in the solid state and do not indicate a possibility for similar structures in solution. Unfortunately, it has not been possible to resolve this question on the basis of solution state spectroscopic data. In the few cases[22] in which spectroscopic data has been obtained for out-of-plane complexes the emphasis has been on characterization as to the stoichiometry or reactivity and not on whether the solution structure mirrors the solid state structures in terms of coordination geometry.

To our knowledge, the combination of crystallographic and spectroscopic data presented here represents the first solid evidence that out-of-plane complexes of electron deficient Lewis acids with enones are possible candidates for reactive intermediates in Diels−Alder reactions. Though chiefly remarkable for its demonstration of an out-of-plane coordination geometry, the crystal structure of **1a**·$TiCl_4$ has many other features of note. The 57.6° Ti−O(1)−C(3)−C(4) dihedral angle indicating the nonplanar coordination geometry is also of interest due to its similarity to dihedral angles found in saturated six-membered rings.[24] Indeed, the chelate has a remarkably chairlike structure (Figure 2), with two of the dihedral angles involving titanium being virtually identical to those found in the saturated carbocyclic ring of the compound (compare entries 1 and 3 with entries 11 and 12 in Table 1). A tilting of the methoxymethyl group out of a purely axial orientation, illustrated by the unusually small[25] −61.9° O(1)−C(3)−C(4)−C(14) dihedral angle, is doubtless a consequence of the thermodynamic preference for an in-plane complexation geometry. That these structural features are carried over to the solution state is suggested by the difference NOE studies described above. A tilt of the methoxymethyl group results in an increase in the distance between the allylic bridgehead proton and the methylene protons of the methoxymethyl group, leading to the expectation of a somewhat attenuated NOE enchancement between these sites in **1a**·$TiCl_4$

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(18) For a recent discussion of the issue of *s-cis* and *s-trans* enone geometries in esters, see Shida, N.; Kabuto, C.; Niwa, T.; Ebata, T.; Yamamoto, Y. *J. Org. Chem.* **1994**, *59*, 4068.

(19) Along similar lines, Yamamoto and co-workers suggested the involvement of an out-of-plane coordinated aluminum Lewis acid to explain stereochemical results in the additions of organometallics to complexes of ketones with methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD): Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573. That a sterically driven out-of-plane complexation is reasonable for this Lewis acid was confirmed by a crystal structure of the methyl *p*-toluate−MAD complex, in which a 50° dihedral angle is seen for Al−O═C−OMe: Shreve, A. P.; Mulhaupt, R.; Fultz, W.; Calbrese, J.; Robbins, W.; Ittel, S. D. *Organometallics* **1988**, *7*, 409.

(20) In addition to leading references in ref 4, see the following work for the only *ab initio* study which we are aware of dealing with $TiCl_4$. Unfortunately from the standpoint of the work described here, the authors do not explictly discuss energetic differences between in-plane and out-of-plane coordination geometries. Branchadell, V.; Oliva, A. *J. Am. Chem. Soc.* **1992**, *114*, 4357.

(21) Search performed on the Cambridge Structural Database, version 5.08, on Ti−O═C with the carbon constrained to be three coordinate. The dihedral angle determined in the current work was included in the calculation of the fraction of compounds having >45° dihedral angle. The references are arranged in order of decreasing Ti−O═C−Y dihedral angle, with the dihedral angle given in parentheses at the end of the citation. Only the larger of the dihedral angles is given for compounds with multiple Ti−O═C interactions. In those cases in which two angles are given, they refer to different compounds reported in the same paper, or to different crystalline forms of the same compound. (a) Sobota, P.; Utko, J.; Lis, T. *J. Organomet. Chem.* **1991**, *417*, 389 (86.8°). (b) Yuchi, A.; Shiro, M.; Wada, H.; Nakagawa, G. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 760 (75.7°). (c) Sobota, P.; Utko, J.; Lis, T. *J. Organomet. Chem.* **1993**, *447*, 213 (59.9° and 72.2°). (d) Sobota, P.; Utko, J.; Lis, T. *J. Organomet. Chem.* **1990**, *393*, 349 (68.4°). (e) Poll, T.; Metter, J. O.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 112 (63.6°). (f) Kakkonen, H. J.; Pursiainen, J.; Pakkanen, T. A.; Ahlgren, M.; Tiskola, E. *J. Organomet. Chem.* **1993**, *453*, 175 (34.7° and 63.2°). (g) Utko, J.; Sobota, P.; Lis, T. *J. Organomet. Chem.* **1989**, *373*, 63 (60.6°). (h) Sobota, P.; Szafert, S.; Lis, T. *J. Organomet. Chem.* **1993**, *443*, 85 (57.5°). (i) Bassi, I. W.; Calcaterra, M.; Intrito, R. *J. Organomet. Chem.* **1977**, *127*, 305 (45.7°).

(22) In addition to ref 21f, see: (a) Albanese, J. A.; Staley, D. L.; Rheingold, A. L.; Burmeister, J. L. *Inorg. Chem.* **1990**, *29*, 2209 (43.7°). (b) Bachand, B.; Belanger-Gariepy, G.; Wuest, J. D. *Organometallics* **1990**, *9*, 2860 (36.7°). (c) Oppolzer, W.; Rodriquez, I.; Blagg, J.; Bernardinelli, G. *Helv. Chim. Acta* **1989**, *72*, 123 (31.2°).

(23) Instances in which the shorter Ti−O═C bond is to the carbonyl bound with a more out-of-plane coordination geometry: refs 21a−c,e−g and 22b. In ref 21h the carbonyl which has a lesser out-of-plane coordination geometry has the shorter bond (by 0.025 Å).

(24) The C−C−C−C dihedral angle in cyclohexane is 56.4°, as calculated using PCModel, version 3.3, Serena Software, Bloomington, IN.

(25) The Cambridge Structural Database (version 5.08) was searched for 6,6-dialkyl-2-cyclohexenones possessing no additional ring $sp^2$ centers and lacking heteroatom substituents in the 2-, 3-, or 4-positions; 22 structures were located. The absolute values of the larger of the two O−C(1)−C(6)−C(alkyl) dihedral angles ranged from 64.9° to 112.6°, with an average of 93.0° ± 13.0°. Absolute values of O═C−C═C dihedral angles ranged from 145.9° to 177.6° with an average of 167° ± 8°.

as compared to **1a**. This is exactly what is observed, with the smaller NOE enhancement in the complex (2.9%) being consistent with a larger distance between the target protons than in the free enone (5.4% enhancement). The 2.9% enhancement found for **1a**·$TiCl_4$ is, however, large enough that one may confidently assign a axial/pseudoaxial orientation of the methoxymethyl group and thus an out of plane coordination geometry for the titanium as seen in the crystal structure. The deformation of the cyclohexenone ring resulting from the tilt of the methoxymethyl group is not sufficiently great to twist the carbonyl and olefin out of conjugation to a substantially greater extent (O═C—C═C dihedral angle 156.6°, entry 8, Table 1) than is sometimes observed for structurally similar enones.[25] There is only one previous example of an X-ray crystal structure of a simple enone with a titanium-based Lewis acid: that of 2-methyl-2-cyclpentenone with $TiCl_4$.[26] The Ti—O bond length of 2.004 Å in this in-plane complex (Ti—O═C—$CH_2$ dihedral angle of 17.3°) is quite comparable to the 2.024 Å observed for **1a**·$TiCl_4$, indicating that the “unfavorable” coordination geometry has not necessarily resulted in a longer, weaker bond.[27]

There is no doubt that coordination of a Lewis acid to a carbonyl oxygen of an enone in an in-plane geometry will lead to a profound increase in its reactivity in Diels—Alder reactions. The effects of such coordination on the magnitudes of orbital coefficients have been demonstrated in calculations by Houk and co-workers, and the consequences of these changes were clearly correlated with experimental observations.[28] However, while we fully accept the reality of activation *via* in-plane coordination geometries, we see no reason why coordination in out-of-plane geometries should not also lead to significant increases in reactivity; given the orbitally controlled nature of the Diels—Alder reaction, it is difficult to conceive that the direct perturbation of the $\pi$-system represented by coordination of a Lewis acid in an out-of-plane geometry would not have an effect on the reactivity. This viewpoint is entirely supported by the results reported here. Childs and co-workers have proposed a ranking of Lewis acidities derived from the magnitudes of the complexation induced chemical shift changes of the $\beta$-enone protons of a number of unsaturated carbonyl compounds.[29] The validity of this Lewis acidity scale has been bolstered by the demonstration of a good qualitative correlation between NMR shift data and the heats of formation of the enone—Lewis acid complexes,[30] as well as by calculational work[31] and reactivity studies by Laszlo.[32] It is unlikely that measured Lewis acid-induced $\Delta\delta$ values of $\beta$-enone protons are *generally* useful indicators for enone reactivity; as noted by Childs, the magnitudes of these changes vary depending on the particular substrate. However, in the present instance, in which the enones being compared are diastereomers, the direct correlation of $\Delta\delta$ values of the $\beta$-enone protons to the strength of the coordinated Lewis acid and the consequent reactivity of the complex seems reasonable. The greater magnitude of $\Delta\delta$ for the $\beta$-enone proton of **1a**·$TiCl_4$ as compared to that of **1e**·$TiCl_4$ leads to the conclusion that *the out-of-plane $TiCl_4$ in **1a**·$TiCl_4$ is a stronger Lewis acid than the in-plane $TiCl_4$ in **1e**·$TiCl_4$.* Further support for the greater Lewis acidity of $TiCl_4$ in an out-of-plane coordination geometry is provided by a comparison of the changes in carbonyl stretching frequencies upon complex formation; the $\Delta\nu_{C=O}$ for **1a** ($-103$ cm$^{-1}$) is quite large,[33] and a full 24 cm$^{-1}$ larger than the $\Delta\nu_{C=O}$ of $-79$ cm$^{-1}$ seen for **1e**, suggesting a lower C═O bond order, and a more allyl cationlike character for the enone. The apparent greater Lewis acidity of the out-of-plane $TiCl_4$ leads to the prediction of a greater reactivity of **1a**·$TiCl_4$ in Diels—Alder reactions—a prediction which has been conclusively validated (in advance) by our previous kinetic studies on the reactivities of **1a**·$TiCl_4$ and **1e**·$TiCl_4$ with cyclopentadiene.[7]

It would be satisfying to be able to state that the results presented here indicate a dominant role for out-of-plane coordination geometries in Lewis acid-mediated Diels—Alder reactions; however, this would clearly constitute an overstatement. The product distribution resulting from any reaction which may proceed through multiple pathways involving rapidly equilibrating conformers or complexes will be a reflection of the relative proportions of the reactive species and their relative reactivities.[5] *If* our reactivity studies of compounds **1a** and **1e** could be extended to all enones, then the 6-fold thermodynamic preference for an in-plane coordination geometry, combined with the 15-fold preference for reaction from an out-of-plane coordination geometry, would result in an overall 2.5-fold preference for product formation from out-of-plane complexes; this would indicate a dominant, but not overwhelming, role for out-of-plane reactive geometries. However, the thermodynamic preference for in-plane vs out-of-plane coordination geometries is likely to vary substantially depending on the particular substrate and Lewis acid employed, and this preference cannot be confidently predicted at this point. As a consequence, we cannot definitively assign a preeminant role to out-of-plane reactive geometries in Diels—Alder reactions; we can only say with surety that such geometries are quite reasonable.

## Conclusions

The results presented here tie together crystallographic and spectroscopic data to demonstrate the viability of out-of-plane coordination geometries in enone—$TiCl_4$ complexes in the solid and solution states. Competition titration studies indicate that, as would commonly be assumed, the in-plane complex **1e**·$TiCl_4$ is more stable (~6-fold at room temperature) than the diastereomeric out-of-plane complex **1a**·$TiCl_4$. However, comparison of spectroscopic changes upon complex formation indicate a greater Lewis acidity of $TiCl_4$ in an out-of-plane coordination geometry and lead to the expectation that the complex **1a**·$TiCl_4$ should be more reactive than **1e**·$TiCl_4$ in Diels—Alder reactions. This expectation has been confirmed by the observed 15-fold greater reactivity

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of **1a**·$TiCl_4$ with cyclopentadiene. While these results do not prove that reaction by way of out-of-plane coordination geometries represents the dominant pathway in all titanium-derived Lewis acid-mediated Diels−Alder reactions, they do indicate this as a very plausible possibility for some substrates. Factors which determine the liklihood of this pathway are likely to be dependent on both substrate and Lewis acid structure and are as yet difficult to predict definitively; however, the probability of such structures seems higher in the cases of electron rich carbonyl compounds such as esters and amides. The wide utility of such substrates in Diels−Alder reactions make it of particular importance to take into account the possibility of out-of-plane coordination geometries in the design of chiral Lewis acids. Finally, it should be emphasized that these results pertain to titanium tetrachloride and its derivatives; whether other electron deficient Lewis acids may also react by out-of-plane geometries remains to be determined.

## Experimental Section

All glassware was oven-dried or flame-dried before use. THF and diethyl ether were distilled from potassium/benzophenone under a nitrogen atmosphere; $CH_2Cl_2$ and $Me_3SiCl$ (TMSCl) were distilled from $CaH_2$ under a nitrogen atmosphere. Diisopropylamine and iodopropane were purchased from Aldrich Chemical Co. and distilled under a nitrogen atmosphere before use. $TiCl_4$ was purchased from Aldrich Chemical Co. and was distilled and stored under a nitrogen atmosphere for no more than two days before use. 2,2′-Dipyridyl diselenide[34] and 2,2′-pyridylselenyl bromide[35] were prepared according to literature procedures. Flash column chromatography was carried out on 230−400 mesh silica gel; radial chromatography was performed on a Chromatotron (Harrison and Harrison) using Merck grade 60PF$_{254}$ silica gel coated plates. Combustion analyses were performed by Atlantic Microlab Inc. laboratories.

**6-[2-(*N*,*N*-Diethylamino)ethoxy]-1,2,3,4-tetrahydronaphthalene (2b)**. 5,6,7,8-Tetrahydro-2-naphthol (3.9919 g, 26.936 mmol) was dissolved in 5 M aqueous KOH solution (17 mL, 85 mmol) at room temperature. *N*,*N*-diethyl-2-chloroethylamine hydrochloride salt (15.0319 g, 87.344 mmol) was added in small portions over a period of 4 h, simultaneously adding enough 5 M aqueous KOH solution to maintain the pH at >13. The reaction mixture was extracted with ether (3 × 50 mL), and the combined organic layers were washed with 1 M aqueous HCl solution (5 × 25 mL). The combined aqueous phases were basified to pH > 13 with the addition of concd aqueous KOH solution, and the mixture was extracted with ether (3 × 50 mL). The ether was dried ($Na_2SO_4$) and evaporated to give a crude oil which was distilled (Kugelrohr, oven temp = 115 °C/0.05 mmHg) to afford pure **2b** (6.4806 g, 97%) as a colorless oil. $^1H$-NMR ($CDCl_3$): $\delta$ 6.91 (d, 1H, $J$ = 8.6 Hz), 6.59−6.65 (m, 2H), 3.97 (t, 2H, $J$ = 6.4 Hz), 2.82 (t, 2H, $J$ = 6.4 Hz), 2.57−2.70 (m, 8H), 1.74 (m, 4H), 1.04 (t, 6H, $J$ = 7.0 Hz). $^{13}C$-NMR ($CDCl_3$): $\delta$ 156, 138, 130, 129, 114, 112, 66, 52, 47, 29, 28, 23.2, 22.9, 12. IR (KBr, neat): 1611, 1503, 1263, 1040 cm$^{-1}$. Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.75; H, 10.12; N, 5.61.

**2-[2-(*N*,*N*-Diethylamino)ethoxy]-1,4,5,6,7,8-hexahydronaphthalene (3b).** A solution of **2b** (6.2600 g, 25.305 mmol) in THF (15 mL) and absolute ethanol (2.97 mL, 50.607 mmol) were added to a solution of dry THF (32 mL) in liquid $NH_3$ (140 mL, freshly distilled from Na metal) at −78 °C. The cloudy solution was allowed to warm to reflux, and lithium metal (740 mg, 107 mmol) was added piecewise over a period of 3 h, waiting for the blue color to be discharged between additions. After an additional 2 h reflux, the reaction was quenched by the addition of absolute ethanol (20 mL), and the liquid $NH_3$ was evaporated with a warm water bath. Dilution with water (200 mL) was followed by extraction with ether (3 × 100 mL), drying of the organic extracts ($Na_2SO_4$), and concentration. Distillation (Kugelrohr, oven temp = 115 °C/0.05 mmHg) afforded **3b** (5.9982 g, 95%) as a colorless oil. $^1H$-NMR ($CDCl_3$): $\delta$ 4.65 (bt, 1H), 3.77 (t, 2H, $J$ = 6.4 Hz), 2.77 (t, 2H, $J$ = 6.4 Hz), 2.55−2.70 (m, 8H), 1.90 (m, 4H), 1.62 (m, 4H), 1.04 (t, 6H, $J$ = 7.0 Hz). $^{13}C$-NMR ($CDCl_3$): $\delta$ 152, 126, 125, 91, 65, 51, 48, 34, 32, 29.4, 29.0, 23.0, 22.7, 12. IR (KBr, neat): 1703, 1672, 1211, 1043 cm$^{-1}$.

**4,4a,5,6,7,8-Hexahydro-1-propyl-2(3*H*)-naphthalenone (4)**. Compound **3b** (10.5105 g, 42.143 mmol) was dissolved in THF (78 mL), and the solution was cooled to −78 °C under an argon atmosphere. A 2.09 M solution of n-BuLi in hexanes (22.2 mL, 46.4 mmol) was added dropwise, and the resulting clear yellow solution was stirred at −78 °C for 1.25 h. HMPA (8.1 mL, 46.6 mmol) was added dropwise, and the resulting crimson solution was stirred at −78 °C for another 1 h. Iodopropane (4.93 mL, 50.5 mmol) was added slowly and the resulting colorless solution stirred for 10 min before allowing to warm to room temperature over 45 min. After dilution with saturated aqueous NaCl and extraction with ether (3 × 150 mL), the organic extracts were dried ($Na_2SO_4$) and evaporated to afford crude 2-[2-(*N*,*N*-diethylamino)ethoxy]-1,4,5,6,7,8-hexahydro-1-propylnaphthalene (18.85 g). This material was dissolved in absolute ethanol (139 mL), and a 5 M aqueous solution of HCl (139 mL, 695 mmol) was added. After heating to reflux for 45 min the solution was cooled to rt and extracted with ether (3 × 100 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ solution (100 mL) and dried ($Na_2SO_4$), and the solvent was evaporated. Purification by flash chromatography on silica gel using 10% MTBE/hexane gave **4** (5.525 g, 68% from **3b**) as a colorless oil, which was identical spectroscopically to material synthesized by a previous route.[7]

**(1*S**,4a*S**,8a*R**)-3,4,4a,5,6,7,8,8a-Octahydro-1-propyl-2(1*H*)-naphthalenone (5).** Lithium metal (702 mg, 101 mmol) was added to a solution of THF (75 mL) in liquid $NH_3$ (620 mL) at −78 °C, and then the cold bath was removed, allowing the solution to warm to reflux. A solution of **4** (5.5250 g, 28.731 mmol) in THF (30 mL) and t-BuOH (2.28 mL, 28.4 mmol) was added dropwise, and the solution was allowed to stir at reflux for 1 h. The reaction was quenched by the careful addition of saturated aqueous $NH_4Cl$ solution (200 mL), and the liquid $NH_3$ was evaporated. The residue was extracted with ether (4 × 100 mL) and dried ($Na_2SO_4$), and the solvent was evaporated to afford a crude oil, which was purified by flash chromatography on silica gel using 1% MTBE/hexane to afford pure **5** (4.0714 g, 73%). $^1H$-NMR ($CDCl_3$): $\delta$ 2.38 (m, 2H), 0.94−2.1 (m, 14H), 1.04 (m, 6H). $^{13}C$-NMR ($CDCl_3$): $\delta$ 212, 55, 47, 41.99, 41.88, 34, 33, 31, 27, 25.76, 25.65, 20, 14. IR (KBr, neat): 1712 cm$^{-1}$. Anal. Calcd for $C_{13}H_{22}O$: C, 80.36; H, 11.41. Found: C, 80.46; H, 11.35.

**(1*S**,4a*S**,8a*R**)-4a,5,6,7,8,8a-Hexahydro-1-propyl-2(1*H*)-naphthalenone (6).** Diisopropylamine (3.52 mL, 25.14 mmol) was dissolved in THF (63 mL) under a nitrogen atmosphere, and the solution was cooled to 0 °C. A 2.09 M solution of n-BuLi in hexanes (12.0 mL, 25.1 mmol) was added dropwise, and this solution of LDA was cooled to −78 °C. A solution of **5** (4.0714 g, 20.952 mmol) in THF (32 mL) was added dropwise, and the resulting solution was stirred at −78 °C for 1.5 h. TMSCl (5.32 mL, 41.9 mmol) was added in one portion; the solution was stirred at −78 °C for 30 min and was then allowed to warm to rt over 45 min. The solvent and excess TMSCl was evaporated; the residue was diluted with hexane and filtered through a plug of Celite. The hexane was evaporated and the residue distilled (Kugelrohr, oven temp = 100 °C/0.05 mmHg) to afford (1*S**,4a*S**,8a*R**)-1,4,4a,5,6,7,8,8a-octahydro-1-propyl-2-(trimethylsilyloxy)naphthalene (5.5473 g, 99%) as a colorless oil having $^1H$-NMR ($CDCl_3$): $\delta$ 4.82 (m, 1H), 0.95−2.00 (m, 18H), 0.87 (t, 3H, $J$ = 6.9 Hz), 0.15 (s, 9H). A portion of this enol silane (4.4409 g, 16.664 mmol) was dissolved in THF (30 mL), and a 1.61 M solution of methyllithium (11.1 mL, 17.9 mmol) was added quickly. The solution was allowed

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to stir at rt for 1.5 h, and the resulting pale solution was added via syringe to a suspension of 2-pyridylselenyl bromide (4.36 g, 18.4 mmol) in THF (182 mL) at −78 °C. The reaction was allowed to warm to rt over a period of 1 h and was diluted with saturated aqueous $NH_4Cl$ solution (31 mL). Extraction with ether (3 × 100 mL) and drying of the extracts ($Na_2SO_4$) was followed by evaporation and purification of the resultant oil by flash chromatography on silica gel using gradient elution (2% to 20% MTBE/hexanes) to give the 3-(2-pyridylselenide) derivative (4.97 g, 85%). This was dissolved in $CH_2Cl_2$ (170 mL) and cooled to −78 °C, and ozone was bubbled through until a violet color was visible. After stirring an additional 1 h at −78 °C, argon was bubbled through to discharge the violet color, and diethylamine (3.20 mL, 31.0 mmol) was added dropwise. The entire reaction solution was poured into a refluxing solution of $CCl_4$ (450 mL) and diethylamine (1.47 mL, 14.2 mmol) and was stirred at reflux for 1.5 h. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel using 3% MTBE/hexane, followed by radial chromatography to give enone **6** (2.095 g, 77%). $^1$H-NMR ($CDCl_3$): $\delta$ 6.63 (d, 1H, $J = 9.9$ Hz), 5.94 (dd, 1H, $J = 3.3$ Hz, $J = 9.9$ Hz), 2.00−2.15 (m, 2H), 1.75−2.00 (m, 5H), 1.50−1.65 (m, 3H), 1.05−1.45 (m, 5H), 0.90 (t, 3H, $J = 7.3$ Hz). $^{13}$C-NMR ($CDCl_3$): $\delta$ 200, 154, 129, 52, 44, 42, 32, 30, 26.40, 25.99, 25, 18, 14. IR (KBr, neat): 1677.4 cm$^{-1}$. Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.33; H, 10.52.

**(4a*S**,8a*R**)-4a,5,6,7,8,8a-Hexahydro-1-propyl-2-(trimethylsilyloxy)naphthalene (7).** Diisopropylamine (2.02 mL, 14.41 mmol) was dissolved in THF (36 mL) under a $N_2$ atmosphere, and the solution was cooled to 0 °C. A 2.09 M solution of n-BuLi in hexanes (6.87 mL, 14.36 mmol) was added slowly, and the resulting solution of LDA was cooled to −78 °C. Compound **6** (2.3019 g, 11.9704 mmol) was added dropwise as a solution in THF (20 mL), and the reaction was stirred for 1.5 h. Chlorotrimethylsilane (3.04 mL, 23.95 mmol) was added in one portion, and the solution was stirred for 30 min. The cold bath was removed, and the solution was allowed to warm to rt over a period of 30 min. The THF and excess chlorotrimethylsilane were evaporated, and the residue was diluted with hexane and filtered through Celite. The hexane was removed and the residue distilled (Kugelrohr, 90 °C/0.05 mm Hg) to afford **7** (3.3419 g, 100%) as a colorless oil. $^1$H-NMR ($CDCl_3$): $\delta$ 5.70 (dd, 1H, $J = 3.1$ Hz, $J = 9.0$ Hz), 5.47 (d, 1H, $J = 9.0$ Hz), 2.25 (ddd, 1H, $J = 5.6$ Hz, $J = 9.0$ Hz, $J = 11.8$ Hz), 1.65−2.05 (m, 9H), 1.05−1.45 (m, 4H), 0.90 (t, 3H, $J = 6.2$ Hz), 0.15 (s, 9H).

**(1*S**,4a*S**,8a*R**)-4a,5,6,7,8,8a-Hexahydro-1-(methoxymethyl)-1-propyl-2(1*H*)-naphthalenone (1a) and (1*R**,4a*S**,8a*R**)-4a,5,6,7,8,8a-Hexahydro-1-(methoxymethyl)-1-propyl-2(1*H*)-naphthalenone (1e).** Compound **7** (1.1548 g, 4.366 mmol) was dissolved in $CH_2Cl_2$ (11 mL) under a nitrogen atmosphere; the solution was cooled to 0 °C, and a 10.13 M solution of chloromethyl methyl ether (**CAUTION: KNOWN CARCINOGEN**) in dimethoxymethane (0.66 mL, 6.69 mmol) was added in one portion. Freshly sublimed $ZnBr_2$ (100 mg, 0.4 mmol) was added in one portion, the mixture was stirred at 0 °C for 1 min, and then the ice bath was removed, allowing the reaction mixture to warm to rt over 1.5 h. The $CH_2Cl_2$ was removed, and the residue was prepurified by rapid passage through a plug of silica gel using 50% ether in petroleum ether as eluent. The crude product thus obtained was purified, and the diastereomers were separated by radial chromatography using $CH_2Cl_2$:petroleum ether:$CH_3OH$ (94.5:5:0.5) to afford the known[7] **1a** and **1e** in a 3.5:1 ratio, respectively (combined yield 792 mg, 77%). $^1$H and $^{13}$C NMR data for these compounds and their 1:1 complexes with $TiCl_4$ have been reported.[7] Difference NOE experiments on **1a**/**e** and **1a**/**e**·$TiCl_4$ were carried out with 0.10 M solutions which had been prepared from argon-degassed $CD_2Cl_2$. Solution IR data was acquired from 0.10 M $CH_2Cl_2$ solutions.

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