Conversion of meso-alkenes to chiral alkenes via titanocene-catalyzed ring-opening/ring-closing olefin metathesis

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Abstract

The preparation of 7-*anti*-(3-methyl-3-butenyl)norbornene **11** is described. This meso-symmetrical diene underwent ring-opening/ring-closing olefin metathesis catalyzed by bis(cyclopentadienyl)titanacyclobutane **4** to give (1*R**,6*R**,7*S**)-7-ethenyl-3-methylbicyclo[4.3.0]non-2-ene as a single diastereomer. The less-substituted 7-*anti*-(3-butenyl)norbornene **1** did not react selectively at the norbornene double bond. Related 7-ester-substituted norbornenes underwent stoichiometric ring-opening/ring-closing olefin metathesis to give single diastereomers of bicyclic ketones after acidic work-up. Attempts to form a chiral Tebbe-type complex from *ansa*-{2,2'-bis[8-(bicyclo[4.3.0]-nona-1(6),7-dienyl)]-1,1'-binaphthyl}titanium dichloride **18** or a reactive chiral titanium carbene intermediate from its dimethyl derivative **20** were unsuccessful. © 1997 Elsevier Science S.A.

Keywords: Olefin metathesis; Chiral bis(cyclopentadienyl)titanium dichloride; Titanacyclobutanes; Stereoselective synthesis; Titanium; Carbene
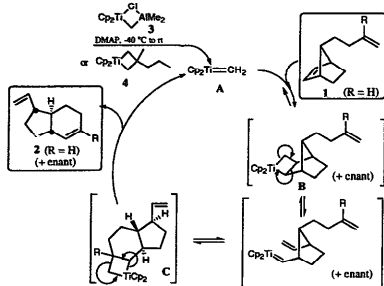
1. Introduction

In the quest for developing new selective carbon–carbon bond forming reactions, the use of the catalytic olefin metathesis reaction has seen increasing application [1]. An early example is Grubbs' stoichiometric ring-opening/ring-closing metathesis by a titanocene carbene in the synthesis of the capnellene ring system [2]. More recently, molybdenum and ruthenium alkylylidenes have been applied to catalytic ring-closing olefin metathesis reactions [3], including applications in the total synthesis of biologically important compounds [4]. To date, the only asymmetric versions of the catalytic olefin metathesis reaction have been in polymerizations [5] and in the kinetic resolutions of racemic dienes through ring-closing olefin metathesis [6]. A key contribution to further the development of an asymmetric catalytic version of this process would be the development of substrates which would enable the enantioselective creation of chiral molecules from achiral starting materials.

We report herein the preparation of a family of meso-symmetrical norbornene derivatives which can

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undergo ring-opening followed by ring-closing olefin metathesis to form new chiral bicyclic structures. With the proper chiral carbene complex such transformations could be performed enantioselectively, and thus could provide a novel application of the chiral titanocene dichloride complexes developed in our [7–9] and other laboratories [10], as well as the recently reported chiral ruthenium and molybdenum alkylidenes [5,6].

We postulated that meso-substrates such as the *anti*-7-butenylnorbornene compound **1** could undergo olefin metathesis as shown in Scheme 1 to yield a single diastereomer of the chiral bicyclic compound **2** through the controlled creation of three stereocenters. The norbornene system was chosen in order to take advantage of the known reactivity of the norbornenyl double bond for ring-opening olefin metathesis [11]. Since syn-7-substituted norbornenes were known to be unreactive in olefin metathesis reactions [12], the anti-7-substituted substrate was targeted. A titanium carbene **A** could be generated either from Tebbe's complex **3** [13] or Grubbs' bis(cyclopentadienyl)titanacyclobutane **4** [14]. Addition of carbene **A** to norbornene **1** would lead to metallocyclobutane **B** (and its enantiomer). Opening metallocycle **B** and reclosing with the appended butenyl double bond would lead to metallocycle **C**, which could regenerate the titanium carbene **A** and the new hydroindene prod-

Scheme 1. Catalytic cycle to convert achiral diene **1** into chiral diene **2**.

uct **2** (as a racemate). The relative 1-6-anti-, 6-7-anti-stereochemistry is set by the original anti-7-butenyl stereochemistry in **1**. If the catalytic cycle is performed using an enantiopure chiral bis(cyclopentadienyl)titanium complex, diastereomeric intermediates would be formed which could lead to enantiomerically enriched product **2**. It was the chemistry of diene **1** that we developed initially.

2. Results and discussion

2.1. Substrate synthesis

The preparation of our key synthetic intermediate **9** for the synthesis of the olefin metathesis substrates is shown in Scheme 2. Norbornenone **5** can be produced in four steps in moderate yield from inexpensive hexachlorocyclopentadiene [15,16]. Conversion of **5** in two steps to a 75:25 ratio of *anti-7:syn-7* was carried out according to Bly et al. [17] with the dissolving metal reduction giving a moderate preference for the desired *anti-7* compound. Although the anti/syn mixture of **7** could be separated chromatographically, it was easier to convert the mixture to the corresponding tosylates **8**
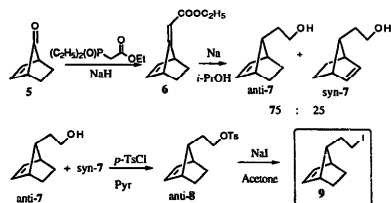
Scheme 2. Preparation of key intermediate **9**.
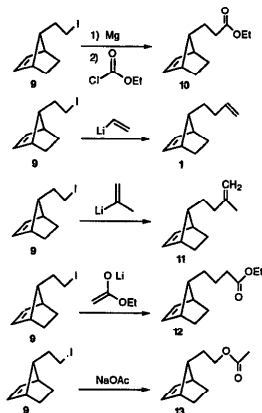
Scheme 3. Preparation of olefin metathesis substrates.

which could be displaced with sodium iodide to give the desired syn-iodide **9** [18] plus an easily separated side-product arising from the rearrangement of the syn isomer [19]. The anti-orientation of the norbornenyl double bond and the 7-(2-iodoethyl) group was readily confirmed through ^{1}H NMR NOE experiments and by comparison with spectra of known 7-substituted norbornenes [17,20].

The key 7-(2-iodoethyl)norbornene **9** was readily converted to the series of olefin metathesis substrates shown in Scheme 3. The ethyl propionate chain was incorporated in norbornene **10** through quenching the Grignard reagent of **9** with ethyl chloroformate. The butenyl- and methylbutenyl-substituted norbornenes **1** and **11** were prepared through the addition of vinyllithium or 2-propenyllithium to iodide **9**. An ester alkylation with the lithium enolate of ethyl acetate provided the butyryl ester **12** while substitution of the iodide in **9** with sodium acetate provided the ethyl-acetate-substituted norbornene **13**. The yields of these readily performed reactions were sufficiently good to provide the quantities of the olefin metathesis substrates needed for the following studies.

2.2. Ring-opening / ring-closing metathesis of 1, 10–13

Based on Grubbs' known stoichiometric ring-opening metathesis of a norbornene followed by a ring-closing addition to an ester [2], we initially studied the stoichiometric reaction of norbornene ester **10** with Tebbe's reagent. Tebbe's reagent **3** was added to a toluene solution of ester **10** and 4-diemethylaminopyri-

dine (DMAP) at −40 °C in a sealable tube and was allowed to gradually warm to room temperature. After heating the mixture at 90 °C for 4.5 h the resulting enol ether was hydrolyzed with 1 N HCl to give bicyclic ketone **14**. As expected from the stereochemistry of the starting meso ester **10**, only a single stereoisomer of hydroindanone **14** was isolated from this stoichiometric reaction. With this promising result for a stoichiometric ring-opening/ring-closing metathesis, we next investigated the potentially catalytic reaction of Tebbe's reagent with the 7-butenylnorbornene (**1**) (Scheme 4).

Excess diene substrate **1**, Tebbe's reagent and DMAP were heated incrementally in an NMR tube. The ^{1}H NMR spectrum at 110 °C indicated that starting material was beginning to disappear. After 4 h most starting substrate still remained and the multitude of the minor new signals indicated the occurrence of non-selective reactions. To check for any inhibition of the olefin metathesis reaction by aluminum complexes, Grubbs' metallacyclobutane **4** [14] was used in place of Tebbe's reagent. In this case a minor amount of what appeared to be cyclized hydroindene **2** could be detected by ^{1}H NMR spectroscopy, but many other side-products were also present and **2** could not be isolated and fully characterized.

We speculated that a metallacyclobutane may be forming preferentially with the terminal olefin rather than the norbornene olefin. In support of this idea, we

allowed Tebbe's reagent and DMAP to react with 10 equiv. of 1-octene in the presence of 10 equiv. of norbornene in methylene chloride from −30 °C to room temperature. Hexanes were added to precipitate the aluminum salts at −30 °C and the ^{1}H NMR spectrum of the concentrated residue was measured. We observed a 3:1 preference for the formation of the metallocyclobutane from 1-octene by comparison with Grubbs' norbornene metallacycle [11]. Since the generation of the titanium carbene on the anti-7-side chain of norbornene could not lead to intramolecular cyclization due to the extremely unfavorable geometry of the needed transition state, any such carbene formed could eventually react through an undesired side pathway.

In order to favor the desired initial carbene reaction at the norbornene double bond, we increased the substitution on the 7-butenyl double bond-converting the side chain to the 3-methyl-3-butenyl side chain. The presence of the 1,1-disubstituted alkene was expected to eliminate any productive olefin metathesis on the side chain [14] and force the initial productive olefin metathesis to occur on the norbornene. In order to confirm the selective reaction at the norbornene double bond, a slight excess of 7-(3-methyl-3-butenyl)norbornene **11** was reacted with Tebbe's reagent in the presence of DMAP in methylene chloride between −78 °C and 0 °C. Hexanes were added at −30 °C to precipitate the aluminum salts which were removed by filtration. The filtrate was concentrated in vacuo at −20 °C to give a thermally and air-sensitive red solid which was identified by ^{1}H and ^{13}C NMR spectroscopy as being the desired metallacycle **15**. This complex was stable enough to measure its NMR spectra at +10 °C, but solutions would decompose upon standing at room temperature.

The ^{1}H NMR spectrum of titanacyclobutane **15** indicated the preferential formation of the norbornene metallacycle over the alkyl metallacycle. By comparison with Grubbs' norbornene titanacyclobutane [11], several diagnostic proton signals confirmed the proposed structure of **15**. A doublet at 3.59 ppm corresponds to H_1 and a doublet of doublets appearing at 3.14 ppm and a doublet of doublets at 1.99 ppm correspond to H_2 and H_3 respectively. The doublet of doublets at 0.19 ppm corresponds to the characteristic H_4 signal. The 1,1-disubstituted vinyl hydrogen signals appear as expected at 4.86 ppm.

In order to establish the ability of metallacycle **15** to undergo the ring-opening/ring-closing metathesis, a sample of this metallacycle in C_6D_6 was examined in a variable-temperature ^{1}H NMR spectroscopy study. Spectra were acquired every 10 °C with the metallacycle only slowly changing up to 100 °C. At 110 °C, a reaction occurred rapidly to afford a ^{1}H NMR spectrum containing hydroindene **16**. New terminal vinyl proton signals at 5.72 ppm and 4.97 ppm, as well as a signal at
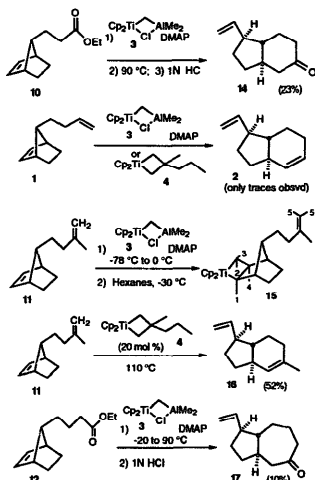
Scheme 4. Reaction of substrates with titanium carbenes.

5.51 ppm for the cyclic olefin appeared as the diagnostic proton signals as the starting metallacycle disappeared.

When excess norbornene substrate 11 was allowed to reacted with Tebbe's reagent, 3, in the presence of DMAP at −20°C to 110°C only minimal reaction occurred. Since the variable-temperature NMR tube reaction had occurred much more cleanly than this attempted catalytic version with Tebbe's reagent, we again suspected that the aluminum salts were interfering with a clean reaction. By heating 11 in the presence of 20 mol% of Grubbs' metallacyclobutane 4, catalytic ring-opening/ring-closing olefin metathesis did take place and the new hydroindene 16 could be isolated in a 52% yield.

We also examined the generality of the stoichiometric cyclization reaction by attempting the stoichiometric formation of heterocyclic compounds as well as increasing the size of the newly formed ring. Ester 12 and acetate 13 were subjected to the conditions established for the cyclization of 10. The stoichiometric reaction of 12 proceeded in low yield to form the bicyclic hydroazulenone 17. The stoichiometric reaction of acetate 13 gave recovered starting material and side-products, including what appeared to be an unisolated vinyl ether resulting from olefination of the ester moiety, but none of the desired cyclization product. Apparently, the sterically less-hindered acetate moiety reacted stoichiometrically with the carbene in preference to the norbornene.

2.3. Attempted chiral carbene formation

From the range of 7-substituted norbornenes studied we found that appendages leading to the hydroindene or hydroindanone ring systems proceeded in good yield. The successful catalytic ring opening/ring-closing metathesis of meso-11 to a single diastereomer of hydroindene 16 with the creation of three new stereocenters exposed the opportunity of using this substrate to study the asymmetric version of the olefin metathesis reaction. By introducing a non-racemic chiral titanocene complex into the olefin metathesis mechanism shown in Scheme 1, a selective formation of one of the two possible diastereomeric complexes B would be possible. Given a selective reaction through one of these diastereomers, enantiomerically enriched product 2 would be formed catalytically. We chose our recently developed and available chiral binaphthyl-bridged ansa-titanocene dichloride 18 [7,8] for our initial studies of the asymmetric olefin metathesis reaction.
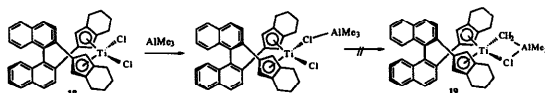
Following a literature procedure for the preparation of the Tebbe complex [21], titanocene dichloride 18 was treated with 4 equiv. of AlMe$_3$ at room temperature, with the exclusion of light for a period of 3 days (Scheme 5). After excess AlMe$_3$ was removed under vacuum the ^{1}H NMR spectrum of the resulting residue revealed the expected doubling of the ligand signals due to removing the C_2-symmetry in 19. Signals for the bridging methylene hydrogen atoms could not be identified, however, and upon reaction of this complex with excess benzophenone in the presence of DMAP from −40 to 60°C in toluene no β-phenyl styrene was detected and dichloride 18 was recovered.

Based on the recovery of the dichloride starting material in the above reactions, we suspected that the reaction between 18 and AlMe$_3$ may have stopped after the initial step of coordination of the aluminum to a chloride, as shown in Scheme 5. To encourage the methyl insertion, a toluene solution of 18 and AlMe$_3$ was simultaneously sonicated and heated to 60°C and monitored by ^{1}H NMR spectroscopy over a period of 1 week. However, the resulting red solution displayed the same ^{1}H NMR spectral characteristics as described above. Several cycles of addition of 2 equiv. of AlMe$_3$, stirring at room temperature for 24 h and pumping dry again only yielded decomposed titanocene.

2.4. Alternate carbene formation attempts

In light of our disappointing results with the attempted formation of a titanium carbene complex via trialkyl aluminum complexation, we examined several alternate methods of carbene formation. One alternate route to 19 required the formation of methylchlorotitanocene [22]. Addition of 1 equiv. of MeLi at 0°C to titanocene dichloride 18 resulted in the formation of dimethyl titanocene 20 and starting material titanocene dichloride 18. Addition of MeMgCl [22] to the titanocene dichloride 18 appeared to result in its reduction to a gray/green color characteristic of Ti^{III} compounds. The reaction mixture decomposed to a black solid when isolation was attempted. Addition of AlMe$_2$Cl [16] to 18 from room temperature to 50°C for up to 1 week resulted only in recovery of starting material.

Petasis and coworkers [23] reported that, upon heating, dialkyl titanocenes can undergo an α-elimination to form a titanium carbene complex which can serve as a convenient alternative to Tebbe's reagent for the olefi-

Scheme 5. Attempted formation of chiral Tebbe reagent.
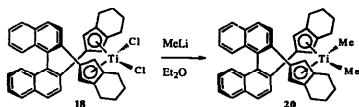
Scheme 6. Preparation of dimethyl titanocene **20**.

nation of carbonyls. To test this route we converted binaphthyl-bridged titanocene dichloride complex **18** to the corresponding dimethyltitanocene complex **20** through the addition of methyllithium, as shown in Scheme 6. The dimethyl complex was isolated in 72% yield and was readily characterized spectroscopically. In the ¹H NMR spectrum of **20** the equivalent methyl groups resonated at −0.05 ppm in C_6D_6 and the signals corresponding to the cyclopentadienyl protons shift to 6.15 and 4.02 ppm as a result of the increased electron density around the metal center donated by the methyl groups. In the ¹³C NMR spectrum the signals arising from the methyl carbon atoms appeared at −12.18 ppm.

To test for the formation of a titanium carbene, dimethyl titanocene **20** was heated in the presence of either norbornene or benzophenone as carbene traps [11,24] in an NMR tube. ¹H NMR spectra were acquired every 10°C up to 130°C. No change was observed in the spectra until 130°C when the titanocene dimethyl complex decomposed. No evidence for the expected carbene reactions with either the norbornene (polymerization) or benzophenone (olefination) was observed and we concluded that this route for carbene generation and reaction was unfruitful.

2.5. Summary

We have established a model molecule (**11**) for studying asymmetric ring-opening/ring-closing olefin metathesis reactions. This meso-symmetrical 7-substituted norbornene reacts in the presence of catalytic amounts of Grubbs' titanacyclobutane **4** to give a new bicyclic hydroindene with the stereocontrolled generation of three new stereocenters. Attempts to form a reactive chiral titanium carbene reagent from the chiral titanocene dichloride **18** or the titanocene dimethyl **20** failed. To determine whether steric or electronic reasons are preventing the formation of the chiral Tebbe complex, we are pursuing the study of related chiral titanocene complexes.

3. Experimental details

3.1. General

For a general description of experimental details see Ref. [24]. Unless otherwise noted, all starting materials

were obtained from commercial suppliers and used without further purification. The following compounds were prepared according to published procedures: 2-norbornen-7-one, [15,16], 7-*anti*-(2-hydroxy-ethyl)bicyclo[2.2.1]-hept-2-ene [17–19], Tebbe's reagent **3** [13], Grubbs' titanacyclobutane **4** [14], *ansa*-[bis-2,2′-(8-(bicyclo[4.3.0]nona-1(6),7-diene))-1,1′-binaphthyl]-dichlorotitanium **18** [7,8].

3.2. 7-anti-(2-Iodoethyl)bicyclo[2.2.1]hept-2-ene (9)

A solution of a 7:3 mixture of 7-*anti*-(2-hydroxy-ethyl)bicyclo[2.2.1]hept-2-ene and 7-*syn*-(2-hydroxy-ethyl)bicyclo[2.2.1]hept-2-ene **7** [17–19] (9.14 g, 66 mmol) in pyridine (53 ml) was added dropwise to a 0°C solution of *p*-toluenesulfonyl chloride (13.9 g, 72.9 mmol) in pyridine (20 ml) to produce a faint pink solution. After 8 h at 0°C, H_2O was added and the solution was extracted with CH_2Cl_2 (3 × 10 ml). The organic layer was washed with H_2O (4 × 20 ml) to remove excess pyridine before drying ($MgSO_4$) and concentrating in vacuo. Residual pyridine was removed on a vacuum line ($P = 0.001$ mmHg) to afford *anti*-**8** as a faint pink solid (18.2 g, 85%): m.p. 157–159°C.

NaI (19.4 g, 129 mmol) was added to a flask charged with *anti*-**8** (12.6 g, 43 mmol) and equipped with a condenser under N_2. Acetone (100 ml) was added and the resulting yellow suspension heated under reflux for 9 h. After cooling to room temperature, the solution was quenched with H_2O (50 ml) and extracted with Et_2O (4 × 20 ml), dried ($MgSO_4$) and concentrated to a pale yellow oil. The crude product was purified (SiO_2, petroleum ether) to give iodide **9** as a clear, colorless oil (6.0 g, 56%). The product consisted of only one isomer (anti) as confirmed by ¹H NMR NOE experiments. ¹H NMR (300 MHz, CDCl₃) δ 6.09 (dd, *J* = 2.5, 2.5 Hz, 2H), 3.10 (m, 2H), 2.59 (br s, 2H), 1.50–1.41 (m, 5H), 1.00–0.89 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 136.91, 59.23, 43.43, 33.66, 28.33, 21.89; IR (thin film) 2959, 2873, 1463, 1426, 1328, 1236, 1174 cm⁻¹; MS, *m/z* (70 eV, rel. intensity) 249 (M⁺¹, 3%), 248 (M, 24.7), 220 (22), 121 (8), 93 (38), 84 (100).

3.3. 7-anti-(Ethyl propionyl)bicyclo[2.2.1]hept-2-ene (10)

To a flask charged with $MgCl_2$ (445 mg, 0.467 mmol) and potassium (315 mg, 0.806 mmol) under argon was added THF (10 ml) at room temperature and the solution was heated under reflux for 3 h. After cooling to room temperature, a solution of 7-*anti*-(2-iodoethyl)bi-cyclo[2.2.1]hept-2-ene (**9**) (200 mg, 0.080 mmol) in THF (20 ml) was added slowly to the activated magnesium over a period of 1 h. After cooling the solution to −78°C, ethyl chloroformate (1.54 ml, 16.1 mmol) was added in one portion. The solution was allowed to warm

to room temperature over 2 h, aqueous 1 N HCl was added and the reaction mixture was extracted with Et$_2$O (3 × 5 ml). The extracts were dried over MgSO$_4$ and concentrated to a pale yellow oil. The crude product was chromatographed (SiO$_2$, petroleum ether, 5% ether–petroleum ether) to give **10** as a clear, colorless oil (41 mg, 26% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.01 (d, $J = 2.5$, 2.5 Hz, 2H), 4.07 (q, $J = 7.5$ Hz, 2H), 2.48 (br s, 2H), 2.18 (t, $J = 7.5$ Hz, 2H), 1.58–1.54 (m, 2H), 1.45–1.39 (m, 1H), 1.37–1.29 (m, 2H), 1.23–1.18 (m, 5H) 0.91–0.87 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.76, 137.18, 60.23, 58.25, 43.76, 32.92, 24.41, 21.73, 14.25; IR (thin film) 2958, 2874, 1736, 1463, 1370, 1329, 1259, 1173 cm^{-1}; MS, m/z (12 eV, rel. intensity) 194 (0.5%), 166 (2).

3.4. 7-anti-(3-Butenyl)bicyclo[2.2.1]hept-2-ene (1)

To a solution of vinyltri(n-butyl)tin (308 μl, 1.04 mmol) in THF (5 ml) at −78 °C under N$_2$ was added n-butyllithium (2.62 M in heptanes, 384 μl, 1.00 mmol) dropwise and the solution was stirred 0.5 h before 7-*anti*-(2-iodoethyl)bicyclo[2.2.1]hept-2-ene (**9**) (200 mg, 0.81 mmol) in THF (3 ml) was added dropwise to produce a pale yellow solution. This solution was allowed to come to room temperature over 6 h before adding H$_2$O (10 ml), extracting with Et$_2$O (3 × 5 ml) and drying over MgSO$_4$. After concentrating in vacuo, the pale yellow oil was carefully chromatographed (SiO$_2$, pentane) to yield **1** as a colorless oil (83.5 mg, 71%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.02 (dd, $J = 2.5$, 2.5 Hz, 2H), 5.76 (ddt, $J = 10.0$, 17.5, 7.5 Hz, 1H), 4.99 (dd, $J = 2.5$, 17.5 Hz, 1H), 4.89 (dd, $J = 2.5$, 10.0 Hz, 1H) 2.48 (br s, 2H), 1.95 (dt, $J = 6.0$, 2.5 Hz, 2H), 1.60–1.45 (m, 3H), 1.10–1.06 (m, 2H), 0.99–0.88 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 139.12, 137.29, 114.13, 58.53, 43.84, 32.19, 28.40, 21.83; IR (thin film) 2954, 2866, 1460, 1259, 1019 cm^{-1}; MS, m/z (12 eV, rel. intensity) 148 (9%), 120 (12), 106 (15).

3.5. 7-anti-(3-Methyl-3-butenyl)bicyclo[2.2.1]hept-2-ene (11)

To a solution of 2-propenyltri(n-butyl)tin (347 mg, 1.05 mmol) in THF (8 ml) at −78 °C under N$_2$ was added dropwise n-butyllithium (2.62 M in heptanes, 400 μl, 1.05 mmol). After stirring 0.5 h at −78 °C, 7-*anti*-(2-iodoethyl)bicyclo[2.2.1]hept-2-ene (**9**) (200 mg, 0.806 mmol) in THF (2 ml) was added dropwise to the 2-propenyllithium solution and the resulting solution was allowed to warm to room temperature over 4 h. The reaction mixture was diluted with H$_2$O, extracted with Et$_2$O (3 × 5 ml) and dried over MgSO$_4$. The crude reaction product was purified (SiO$_2$, pentane) to give **11** as a colorless oil (69 mg, 53%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.09 (dd, $J = 2.5$, 2.5 Hz, 2H), 4.68 (d, $J =$

6.0 Hz, 2H), 2.55 (br s, 2H), 1.95 (t, $J = 2.5$ Hz, 2H), 1.72 (s, 3H), 1.63–1.59 (m, 2H), 1.52–1.48 (m, 1H), 1.22–1.15 (m, 2H), 0.96–0.90 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 138.10, 137.27, 109.91, 58.69, 43.95, 36.13, 31.82, 29.00, 21.83; IR (neat) 2958, 2860, 1649, 1461, 1374, 1329, 1119 cm^{-1}; MS, m/z (70 eV, rel. intensity) 162 (11%), 138 (7), 134 (100), 119 (21).

3.6. 7-anti-(Ethyl n-butyryl)bicyclo[2.2.1]hept-2-ene (12)

To an LDA solution composed of diisopropylamine (1.03 ml, 7.33 mmol) and n-butyllithium (2.62 M in heptanes, 2.77 ml, 7.25 mmol) under N$_2$ in THF (6 ml) was added dropwise ethyl acetate (788 μl, 8.06 mmol) at −78 °C. After 0.5 h, HMPA (1.26 ml, 7.25 mmol) was added slowly to the reaction mixture and, after stirring for 0.5 h, a solution of 7-*anti*-(2-iodoethyl)bicyclo[2.2.1]hept-2-ene (**9**) (200 mg, 0.80 mmol) in THF (1 ml) was added dropwise to the reaction mixture. After gradually coming to room temperature, the colorless solution was stirred for 3 h. The reaction mixture was quenched with H$_2$O (10 ml), the crude product extracted with Et$_2$O (3 × 5 ml) and then dried (MgSO$_4$). The crude product was purified (SiO$_2$, 10% ethyl acetate/petroleum ether) to yield **12** as a clear colorless oil (96 mg, 57%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.02 (dd, $J = 2.5$, 2.5 Hz, 2H), 4.08 (q, $J = 7.5$ Hz, 2H), 2.48 (br s, 2H), 2.23 (t, $J = 7.5$ Hz, 2 H), 1.60–1.52 (m, 4H), 1.21 (t, $J = 7.5$ Hz, 3H), 1.20–1.15 (m, 1H), 1.05–0.99 (m, 2H), 0.91–0.88 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.58, 137.16, 60.05, 58.44, 43.74, 34.44, 28.42, 23.29, 21.70, 14.16; IR (neat) 2957, 2872, 1735, 1465, 1373, 1248, 1169 cm^{-1}; MS, m/z (70 eV, rel. intensity) 208 (39%), 180 (63), 162 (55), 134 (100), 106 (56).

3.7. 7-anti-(2-Acetoethyl)bicyclo[2.2.1]hept-2-ene (13)

A solution of 7-*anti*-(2-iodoethyl)bicyclo[2.2.1]hept-2-ene (**9**) (100 mg, 0.40 mmol) in HMPA (4 ml) was added to sodium acetate (83 mg, 0.80 mmol) and the mixture heated at 100 °C for 8 h under N$_2$. H$_2$O (10 ml) was added and the mixture extracted with Et$_2$O (3 × 5 ml). The organic portion was washed twice with H$_2$O (10 ml), dried (MgSO$_4$), concentrated and purified by chromatography (SiO$_2$, 30% methylene chloride/petroleum ether) to yield **13** as a colorless oil (56 mg, 78%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.05 (dd, $J = 2.5$, 2.5 Hz, 2H), 3.99 (t, $J = 7.5$ Hz, 2H), 2.53 (br s, 2H), 2.02 (s, 3H), 1.59–1.55 (m, 3H), 1.40–1.35 (m, 2H), 0.95–0.92 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 176.53, 137.14, 63.68, 46.10, 43.97, 29.73, 28.14, 21.75; IR (thin film) 2959, 2926, 1740, 1464, 1365, 1240, 1037, 801 cm^{-1}; MS, m/z (70 eV, rel. intensity) 180 (2%), 121 (3), 120 (22), 105 (13), 93 (14).

3.8. Formation of (1R*,6R*,7S*)-7-ethenylbicyclo[4.3.0]non-3-one (14)

In a glove box under N_2, a sealable tube equipped with a vacuum adapter was charged with Tebbe's reagent (150 mg, 0.53 mmol) and transferred to a Schlenk line. Toluene (2 ml) was added and the deep red solution was cooled to −40°C before adding a toluene solution (3 ml) of DMAP (87 mg, 0.71 mmol) and 7-anti-(ethyl propionyl)bicyclo[2.2.1]hept-2-ene (10) (69 mg, 0.35 mmol). The resulting solution was allowed to warm gradually to room temperature over 0.5 h. After stirring for 1.5 h at room temperature, the tube was sealed and heated to 90°C for 4.5 h. The tube was cooled to room temperature opened to air and the contents were diluted with pentane (50 ml). The resulting yellow suspension was stirred at room temperature for 1 h. The suspension was filtered through a small pad of SiO_2 with pentane and the filtrate was concentrated in vacuo. The resulting product was diluted with Et_2O (5 ml) and hydrolyzed with 1 N HCl (3 ml) at room temperature for 3 h. The organic portion was separated, concentrated and chromatographed (SiO_2, 20% ether/petroleum ether) to yield 14 as a clear colorless oil (11 mg, 23% yield). ^1H NMR (300 MHz, CDCl$_3$) δ 5.74 (ddd, J = 16.5, 8.0, 2.0 Hz, 1H), 4.99 (dd, J = 14.5, 9.0 Hz, 1H), 4.93 (dd, J = 14.5, 2.5 Hz, 1H), 2.55–2.52 (m, 1H), 2.50 (dd, J = 4.0, 2.0 Hz, 1H), 2.41 (dd, J = 4.0, 2.0 Hz, 1H), 2.36 (dd, J = 4.0, 2.0 Hz, 1H), 1.14–2.86 (m, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 202.00, 142.50, 114.30, 50.42, 48.56, 47.76, 46.75, 40. 82, 30.90, 30.20, 28.00; IR (neat) 2956, 2868, 1740, 1715, 1460, 1365, 1260 cm^{-1}; MS, m/z (70eV, GCMS, rel. intensity) 164 (21%), 149 (5), 136 (71), 121 (23).

3.9. Formation of bis(cyclopentadienyl)titanacyclobutane 15

To a flask charged with Tebbe's reagent 3 (0.091 g, 0.32 mmol) under N_2 was added a solution of 11 (0.069 g, 0.43 mmol) and DMAP (0.052 g, 0.32 mmol) in methylene chloride (2 ml) at −78°C. The solution was allowed to warm to 0°C and, after 4 h, hexanes were added at −30°C to precipitate the aluminum salts. The mixture was filtered at −30°C and the solvent removed under vacuum at −20°C. The residue was triturated with minimal toluene at −30°C to remove unreacted 11 and the resulting solid was examined by NMR spectroscopy at 10°C and identified as titanacyclobutane 15. This compound was both thermally and air-sensitive. ^1H NMR (300 MHz, 10°C, CDCl$_3$) δ 5.54 (s, 5H), 5.30 (s, 5H), 4.86 (m, 2H), 3.59 (d, J = 9.5 Hz, 1H), 3.14 (dd, J = 11.0, 9.0 Hz, 1H), 2.06 (m, 2H), 1.99 (dd, J = 9.0, 9.0 Hz, 1H), 1.82 (m, 2H), 1.68 (s, 3H), 1.32–1.44 (m, 5H), 1.22 (m, 2H), 0.19 (ddd, 11.0, 9.5, 9.0 Hz, 1H); ^{13}C NMR (75 MHz, 10°C, CDCl$_3$) δ 146.09, 137.62, 109.25, 109.11, 108.54, 72.28, 49.86, 44.57, 43.95, 37.46, 32.37, 27.79, 25.79, 22.42, 21.15.

3.10. Formation of (1R*,6R*,7S*)-7-ethylene-3-methylbicyclo[4.3.0]non-2-ene (16)

Grubbs' reagent 4 (5.4 mg, 0.015 mmol) in toluene (4 ml) was added to a sealable tube charged with 7-anti-(4-methyl-4-butenyl)bicyclo[2.2.1]hept-2-ene (11) (10.0 mg, 0.06 mmol) resulting in a deep red colored solution. The tube was sealed under argon and heated to 110°C in an oil bath for 6 h. After cooling to room temperature, the amber colored solution was diluted with petroleum ether and filtered through a pad of silica gel to remove any traces of the catalyst. The crude colorless oil was concentrated and chromatographed (SiO_2, pentane) to give 16 as a colorless oil (5.0 mg, 52%). ^1H NMR (300 MHz, CDCl$_3$) δ 5.75 (ddd, J = 16.5, 8.0, 2.0 Hz, 1H), 5.51 (br s, 1H), 4.99 (dd, J = 14.5, 9.0 Hz, 1H), 4.89 (dd, J = 14.5, 2.5 Hz, 1H), 2.10–1.06 (m, 11 H), 1.64 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 142.86, 124.61, 113.28, 49.57, 48.04, 44.88, 31.69, 30.29, 28.80, 25.91, 23.26; IR (neat) 3053, 2959, 2874, 1570, 1436, 1185, 1071 cm^{-1}; MS, m/z (70eV, rel. intensity) 162 (11%), 147 (19) 135 (20), 133 (65).

3.11. Formation of 8-ethylene-bicyclo[5.3.0]-deca-3-one (17)

7-anti-(Ethyl 4-butyryl)bicyclo[2.2.1]hept-2-ene (12) was cyclized according to the representative procedure for the catalytic cyclization of 10 (Section 3.3) using 12 (70 mg, 0.36 mmol), Tebbe's reagent 3 (114.8 mg, 0.40 mmol) and DMAP (57.1 mg, 0.47 mmol). The crude product was purified (SiO_2, 20% ether/petroleum ether) to yield 17 as a clear colorless oil (5.8 mg, 9%). ^1H NMR (300 MHz, CDCl$_3$) δ 5.68 (ddd, J = 16.5, 8.0, 2.0 Hz, 1H), 4.95 (dd, J = 14.5, 9.0 Hz, 1H), 4.89 (dd, J = 14.5, 2.5 Hz, 1H), 2.61 (dd, J = 16.0, 2.5 Hz, 1H), 2.49 (dd, J = 16.0, 2.5 Hz, 1H), 0.99–2.30 (m, 13H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 202.00, 142.50, 114.30, 50.42, 48.56, 47.76, 46.75, 40. 82, 30.90, 30.20, 28.00; IR (neat) 2956, 2868, 1740, 1715, 1460, 1365, 1260 cm^{-1}; MS, m/z (70eV, GCMS, rel. intensity) 178 (19%), 163 (2), 151 (6).

3.12. Attempted stoichiometric cyclization of 7-anti-(acetoethyl)bicyclo[2.2.1]hept-2-ene (13)

The stoichiometric cyclization of 7-anti-(acetoethyl)bicyclo[2.2.1]hept-2-ene (13) was conducted according to the representative procedure for the stoichiometric cyclization of 10 (Section 3.3) using 13 (200 mg, 0.90 mmol), Tebbe's reagent 3 (283.5 mg, 0.99 mmol) and DMAP (142.7 mg, 1.17 mmol) or 2-methyl-1-pentene titanacyclobutane (4) (273.1 mg,

0.99 mmol) in toluene (19 ml). According to the ^{1}H NMR spectrum of the crude reaction mixture, no desired [4.3.0]bicycloheptane product could be identified, but recovered **13** and what appeared to be (3-oxa-4-methyl-4-pentenyl-1-yi)bicyclo[2.2.1]hept-2-ene were the major constituents. The presumed olefination product was not, however, isolable for characterization.

3.13. ansa-[2,2'-Bis[8-(bicyclo[4.3.0]-nona-1(6),7-dienyl]i-1,1'-vinaphthyl]dimethyltitanium (26)

To a $-10\,°C$ ether solution (1.65 ml) of **18** [7,8] (100 mg, 0.165 mmol) was added dropwise MeLi (0.94 M in ether, 184 μl, 0.173 mmol) to give eventually a yellow suspension. The suspension was stirred at $-10\,°C$ for 3 h before removing the solvent in vacuo. To the crude yellow solid was added benzene and the suspension was filtered to remove residual LiCl. The mother liquor was pumped to dryness and recrystallized from benzene/hexane to give **20** as a yellow solid (66 mg, 72%): m.p. $260\,°C$ (dec.). ^{1}H NMR (300 MHz, C_6D_6) δ 7.61 (m, 6H), 7.22 (d, $J = 8.5$ Hz, 2H), 7.11, (dd, $J = 7.0$, 7.0 Hz, 2H), 6.83 (dd, $J = 7.0$, 7.0 Hz, 2H), 6.15 (d, $J = 2.5$ Hz, 2H), 4.00 (d, $J = 2.5$ Hz, 2H), 2.99 (m, 4H), 1.28–2.11 (m, 12H), -0.05 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 134.38, 133.19, 132.71, 131.61, 130.93, 128.85, 127.71, 127.44, 127.06, 126.86, 125.57, 125.10, 120.99, 112.40, 111.20, 25.75, 24.21, 23.19, 23.09, -12.18 ; IR (C_6D_6) 2956, 1633, 1505, 1413, 1261, 1095, 1016 cm^{-1} ; MS, m/z (70 eV, rel. intensity) 571 (M$^+$ + 5, 100%), 490 (22), 370 (10), 281 (13), 207 (72).

Acknowledgements

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