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Synthesis of Highly Functionalised Enantiopure Bicyclo[3.2.1]-octane Systems from Carvone

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Abstract: The commercially available monoterpene carvone has been efficiently converted into the tricyclo[3.2.1.$0^{2.7}$]octane and bicyclo[3.2.1]octane systems characteristic of some biologically active compounds. The sequence used for this transformation involves as key features an intramolecular Diels-Alder reaction of a 5-vinyl-1,3-cyclohexadiene and a cyclopropane ring opening.

Keywords: Carvone, Diels-Alder reaction, cyclopropane cleavage, 5-vinyl-1,3-cyclohexadiene, samarium diiodide, bicyclo[3.2.1]octane, tricyclo[3.2.1.$0^{2.7}$]octane

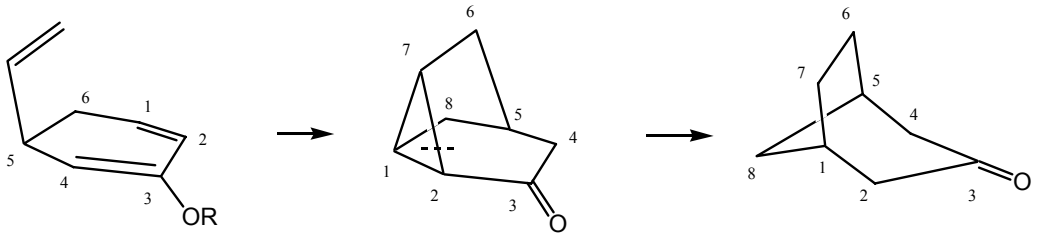
Introduction

The bicyclo[3.2.1]octane ring system is the basic framework of many important biologically active natural compounds, particularly tri- and tetracyclic sesqui- and diterpenes [1]. The widespread occurrence of this common structural motif in so many biologically active natural products has stimulated the preparation of simple non-natural structures containing the carbo-bicyclic system with variable functional diversity, many of which have also shown relevant biological activity. A logical consequence of the interest in this type of compounds has been the development of a plethora of synthetic methods for making bicyclo[3.2.1]octanes [2], in many cases appropriately functionalised to be useful intermediates in the synthesis of the more complex natural products containing this bicyclic

subunit. Some of the more efficient methodologies developed for the preparation of the bicyclo[3.2.1]octane system are based in the selective fragmentation of different types of functionalised tricyclo[3.2.1.$0^{2.7}$]octane derivatives, whose tricyclic cores have been constructed basically using two methods, an intramolecular cyclopropanation of a double bond [2,3], or a bicycloannulation of cyclic dienolates with various Michael acceptors [2,4].

In this report we describe the preparation of several enantiopure bicyclo[3.2.1]octane systems **3** using an alternative approach for the construction of the bicyclic skeleton, one based on an intramolecular Diels-Alder (IMDA) reaction of a 5-vinyl-1,3-cyclohexadiene **1** and the regioselective cleavage of the obtained tricyclo-[3.2.1.$0^{2.7}$]octan-3-one intermediate **2** (Scheme 1) [5].

Scheme 1



5-Vinyl-cyclohexa-1,3-diene (**1**) Tricyclo[3.2.1.$0^{2,7}$]octane (**2**) Bicyclo[3.2.1]octane (**3**)

It must be mentioned that although several intramolecular cycloadditions involving 5-vinyl-1,3-cyclo-hexanedienes have been described in the literature [6], these types of Diels-Alder reactions have not been previously evaluated for their synthetic utility. Only recently, and while this work was in progress, Trauner described the preparation of several substituted tricyclo[3.2.1.$0^{2.7}$]oct-3-enes *via* IMDA reactions of 5-vinyl-1,3-cyclohexadienes. He has also called attention to the synthetic potential of this reaction in the synthesis of several polycyclic natural products and suggested the possible implication of such a reaction in their biosynthesis [7].

Results and Discussion

Carvone (**4**) was used as the starting chiral material with the objective of preparing the bicyclo[3.2.1]octane framework in enantiomerically pure form. This is a monoterpene, commercially available in both enantiomerically pure forms, (*R*)-(-)- and (*S*)-(+)-carvone, that has been widely used by us [8] and others [9] as a chiral starting material in the synthesis of numerous natural products.

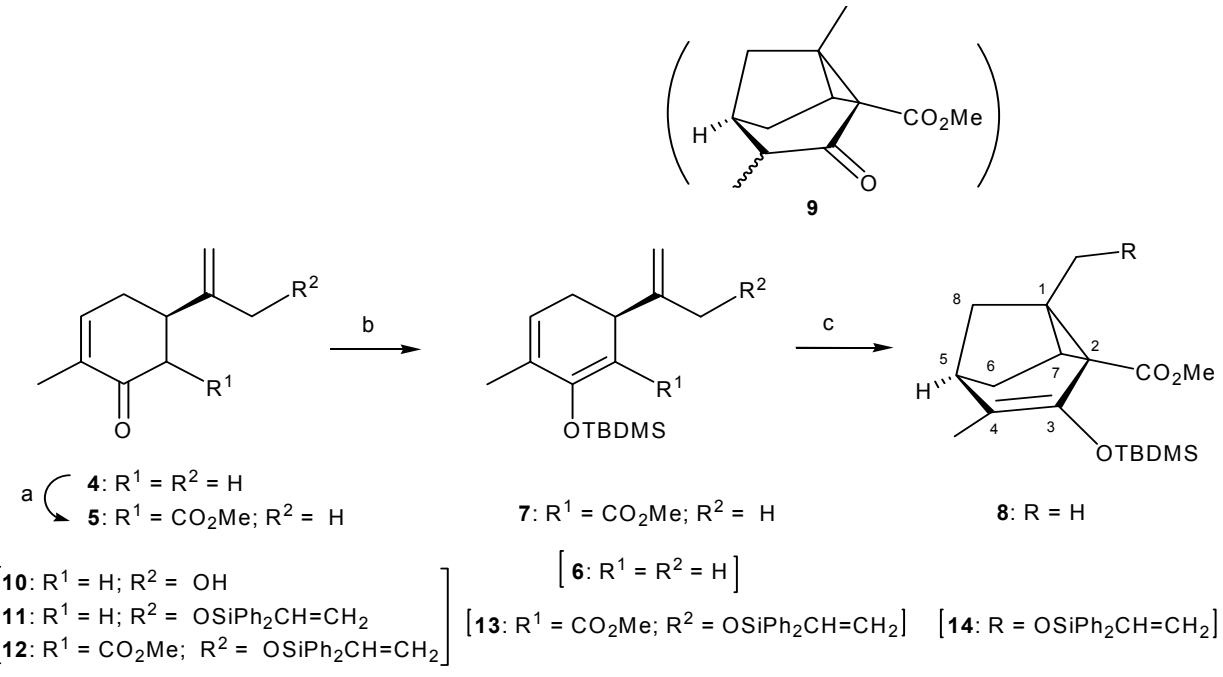
The synthesis starts with the conversion of carvone (**4**) into the β-keto ester **5** using Mander´s methoxycarbonylation procedure [10]. Thus, reaction of methyl cyanoformate with the kinetic lithium enolate of **4,** generated by treatment with LDA in THF at low temperature, afforded the β-keto ester **5** in very high yield (Scheme 2). Although irrelevant from the synthetic point of view, compound **5** seems to exist basically in only one tautomeric form in which the methoxycarbonyl groups occupies

the equatorial position, as suggested by the coupling constant pattern observed in the ^{1}H-NMR spectrum for H-1 (a singlet with J = 13 Hz).

It should be pointed out that the methoxycarbonyl group was introduced at the C-2 position of carvone with the dual purpose of installing a versatile functional group for further functionalization of the target bicyclic systems as well as to avoid diene isomerisation during the subsequent Diels-Alder step. In fact, attempts to directly elaborate the diene moiety from **4**, e.g. compound **6**, always afforded a mixture of isomeric cyclohexadienes under different experimental conditions. With the methoxycarbonyl group in place, the regioselective formation of the silyloxy diene moiety was readily accomplished by enolization of **5** by treatment with lithium *bis*(trimethyl)silylamide and capture of the enolate with *tert*-butyldimethylsilyl triflate. Conversion of (*R*)-carvone into the *tert*-butyldimethylsilyl enol ether **7** was thus accomplished in *ca*. 82% overall yield.

The 5-vinyl-1,3-cyclohexadiene moiety of **7** underwent an intramolecular Diels-Alder reaction smoothly and efficiently upon heating a degassed anhydrous toluene solution of this compound and a small amount of propylene oxide in a sealed ampoule at 190 ºC for 48 h. Compound **8**, containing the tricyclo[3.2.1.0$^{2.7}$]oct-3-ene system, was thus obtained in 80% of yield after purification by column chromatography. It must be mentioned that in the absence of propylene oxide as acid scavenger, both the starting *tert*-butyldimethylsilyl enol ether **7** and the Diels-Alder adduct **8** were partially hydrolyzed to the β-keto ester **5** and a mixture of epimeric tricyclo-ketones **9**, respectively. The structure and stereochemistry of the adduct **8** were confirmed by its spectroscopic data, particularly the ^{1}H- and ^{13}C-NMR signals which were unambiguously assigned using HMQC and NOESY experiments [11].

Scheme 2

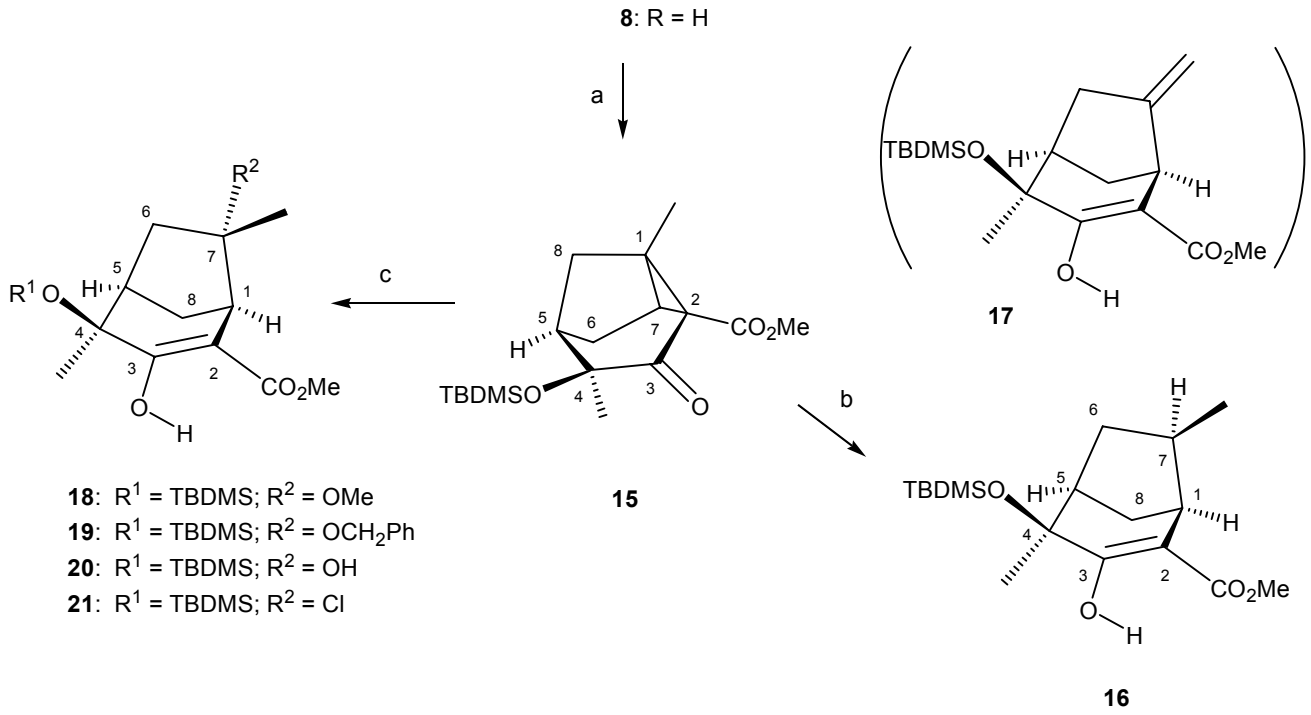


Reagents and conditions: (a) LDA, THF, -78ºC then $CNCO_2CH_3$-HMPA. (b) $LiN[Si(CH_3)_2]_2$, THF, -78ºC then TBDMSOTf. (c) Toluene, 190 ºC, 48h.

It is interesting to note that the intramolecular Diels-Alder reaction of the 5-vinyl-1,3-cyclohexadiene moiety is strongly preferred to other alternative intramolecular cycloadditions that were also attempted, in spite of the highly strained transition state presumably involved. Thus, when compound **13** (and also the corresponding dimethyl(vinyl)silyl analogue, **13** with $R^2 = OSiMe_2CH{=}CH_2$), readily prepared from hydroxycarvone **10** as described in the Experimental section, was heated in toluene under the same conditions described above for **7**, only the Diels-Alder adduct **14** was formed, without any appreciable amounts of the adduct resulting from the alternative intramolecular cycloaddition of the 1,3,10-undecatriene moiety being observed [12].

Having completed the construction of the tricyclo[3.2.1.$0^{2.7}$]octane framework, and prior to the opening of the cyclopropane ring, we decided to use the existing *tert*-butyldimethylsilyl enol ether moiety to incorporate an additional oxygenated function that could provide sites for further functionalization of the final bicyclo[3.2.1]octane system. In this regard, it was decided to transform the adduct **8** into the ketone **15** (Scheme 3).

Scheme 3



Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, -30ºC. (b) SmI_2, THF-^{t}BuOH, -40ºC. (c) MeOH, HCl, rt for **18**; $PhCH_2OH$, PTSA, rt for **19**; H_2O-THF, HCl, rt for **20**;.THF-HCl, rt for **21**.

This transformation was accomplished in a single step by treatment of **8** with *m*-CPBA in methylene dichloride at -30 ºC. Under these conditions, epoxidation of the double bond took place from the less hindered β-face initially giving the corresponding β-epoxide, which directly rearranged

with concomitant migration of the *tert*-butyldimethylsilyl group to give the ketone **15**. The structure and relative stereochemistry of this compound were established by a detailed analysis of its NMR data. In particular, protons H-8β and H-6α gave strong correlation signals with the *tert*-butyl protons and the methyl protons at C-4, respectively, unequivocally stabilising the spatial orientation of both groups at C-4.

With the tricyclic system **15** at hand, we investigated the opening of the cyclopropane ring in order to elaborate the bicyclo[3.2.1]octane framework. In the literature, dissolving metal reductions with metal-ammonia systems has been the most frequently used method for the cleavage of cyclopropyl ketones [2]. The electron transfer homogenous reagent samarium(II) iodide has been less often used for this purpose, although some examples of samarium(II)-mediated cyclopropane cleavage of rigid cyclopropyl ketones have been described [2,13]. When applied to the opening of **15**, a regioselective cleavage of the C_1-C_2 bond of the cyclopropane ring took place to cleanly afford the bicyclo[3.2.1]octane ring system (Scheme 3). It was found that the best results were obtained by treatment of a cooled (-40 ºC) solution of **15** in a 9:1 mixture of THF and *tert*-butanol with a stock solution of samarium(II) diiodide in THF. An 80% yield of the β-keto ester **16** was obtained under these conditions, which both as a solid and in solution, basically exists in the enol tautomeric form. It is noticeable that elimination of the 4-silyloxy moiety was never observed, even when an excess of the reducing reagent was used. It is also interesting to note that when the samarium(II)-mediated cyclopropane cleavage was effected in the absence of a protic solvent, the reaction was not so clean and the compound **17** was the major product obtained. The formation of this compound is easily explained by formation of a radical intermediate at C-7 and subsequent hydrogen abstraction from the adjacent methyl group. The stereochemistry of **16** was unambiguously assigned on the basis of coupling constant and NOESY data. Particularly relevant was the presence of a strong NOESY correlation of methyl protons at C-7 to methyl protons of the ester moiety at C-2, which provided evidence of the (*R*)-configuration at C-7.

The carbobicyclic ring system formed in the above cyclopropane cleavage reaction not only constitutes the characteristic substructural fragment of some natural compounds that have been found to display important biological activity [14], but is also the basic core structure of carbo-tropanes, a group of synthetic compounds that are potent inhibitors of the dopamine transporter [15]. Thus, the readily prepared enantiomerically pure compound **16** may be potentially used as an adequate scaffold from which to append "side chain" groups, thereby generating small libraries with functional and structural diversity that may be evaluated for biological activity.

In addition to the above radical opening of the cyclopropane ring of **15**, we also evaluated the acid catalysed nucleophilic addition reaction to the cyclopropyl ketone moiety as an alternative procedure for the tricyclo[3.2.1.$0^{2.7}$]octane-to-bicyclo[3.2.1]octane interconversion. It was found that a rapid and efficient opening of the cyclopropane ring of **15** took place upon treatment with different nucleophilic reagents in the presence of an acid catalyst. Thus, treatment of **15** with methanol and catalytic *p*-toluenesulphonic acid (PTSA) or HCl at room temperature afforded a high yield of methyl ether **18**, formed by acid initiated homoconjugate addition of methanol to the cyclopropyl ketone moiety. The

addition of methanol takes place regio- and stereoselectively from the back of C-1, affording the bicyclo[3.2.1]oct-1-ene system stereoselectively functionalized at C-7. The stereochemistry of **18** was determined by comparison of its spectroscopic data with those of **16** and confirmed by a NOESY experiment. Thus, the H-8β proton gives a strong correlation signal with the protons of the methoxy group while the protons of the methyl group at C-7 give strong correlation signals with both the protons of the methoxycarbonyl group and the H-6β proton.

Similar results were obtained with other nucleophiles. Thus, benzyl ether **19**, alcohol **20** and chloride **21** were readily formed by treatment of **15** with benzyl alcohol and catalytic PTSA in CH_2Cl_2 (80% yield), water and catalytic HCl in THF (80% yield), and concentrated HCl in THF (86% yield), respectively. It should be mentioned that in the latter two cases, *ie*., compounds **20** and **21**, partial reversion to the starting tricyclic compound **15** occurs on attempted chromatographic purification on silica gel. It is likely that this particularly easy interconversion is facilitated by the homoaromatic character of the carbocationic intermediate generated.

Conclusions

In brief, the results obtained show the viability of the synthetic approach based on the combination of an intramolecular Diels-Alder reaction of a 5-vinyl-1,3-cyclohexadiene and a cyclopropane ring opening for the preparation of the bicyclo[3.2.1]octane framework. The application of this strategy, starting from carvone, has allowed us to prepare several enantiopure, highly functionalised, bicyclo[3.2.1]oct-1-ene derivatives.

Acknowledgments

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Experimental

General

Melting points were determined using a Buchi hot-stage apparatus. Optical rotations were determined using a 5 cm path length cell. $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. All NMR spectra were recorded on a Bruker AVANCE 300 DRX spectrophotometer in $CDCl_3$ solutions (at 300 MHz for ^1H and 75 MHz for ^{13}C). Complete assignment of the NMR data for most of the compounds described in the experimental section was done on the basis of a combination of HMQC, HMBC and NOESY 2D experiments. Mass spectra were obtained by electron impact (EI) at 70 eV. IR spectra were measured as KBr pellets or liquid films. All reactions were carried out under an inert atmosphere

of dry argon, using oven-dried glassware and freshly distilled and dried solvents. Column chromatography refers to flash chromatography and was performed on Merck silica gel 60, 230-400 mesh.

(5R,6R)-2-(tert-Butyldimethylsilanyloxy)-6-isopropenyl-3-methylcyclohexa-1,3-dienecarboxylic acid methyl ester (**7**). A solution of commercial (*R*)-(-)-carvone (3.98 g, 25.9 mmol) in THF (20 mL) was added dropwise to a solution of LDA in THF (44.3 mL of a 0.7 M solution, 31.1 mmol) at -78 ºC. The reaction mixture was allowed to warm to -10 ºC and stirred at this temperature for 1 h, then cooled to -78 ºC and HMPA (4.5 mL) was added, followed by methyl cyanoformate (3.2 mL, 38.9 mmol). After 30 min the reaction mixture was poured into saturated NH_4Cl solution and extracted with ether. The combined organic layers were washed with brine and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was purified by column chromatography, using 9:1 hexane-ethyl acetate as eluent, to give *β-keto ester* **5** (5.4 g, 98%) as an oil, bp 103 ºC (2 mmHg) [lit. 142 (15 mmHg)] [10]; $[\alpha]_D^{18}$ -30 (c 2.8, $CHCl_3$); IR (film) 3040-2800, 1743, 1672, 1360, 1260, 900 cm^{-1}; ^{1}H-NMR δ 6.72 (1 H, m, H-4), 4.80 (2 H, m, H-2´), 3.69 (3 H, s, OMe), 3.46 (1 H, d, *J* 13 , H-1), 3.1 (1 H, ddd, *J* =13, 10.5 and 5 Hz, H-6), 2.5-2.2 (2 H, m, H-5), 1.76 (3 H, m, Me-3) and 1.72 ppm (3 H, s, Me-1´); ^{13}C-NMR δ 15.71 (C_3-Me), 19.66 (Me-$C_{1'}$), 30.36 (C_5), 45.65 (C_6), 51.97 (CO_2CH_3), 58.23 (C_1), 112.80 ($C_{2'}$), 134.8 (C_3), 144.48 (C_4), 144.55 ($C_{1'}$), 170.32 (CO_2) and 194.74 ppm (C_2); MS *m/z* (CI) 210 (M^++2, 10), 209 (M^++1, 100), 178 (10), 177 (90), 167 (75), 149 (46), 135 (15), 123 (15) and 51 (3).

A solution of β-ketoester **5** (500 mg, 2.4 mmol) in THF (6 mL) was added dropwise to a 1M solution of lithium *bis*(trimethyl)silylamide in hexane (3.2 mL, 3.2 mmol) cooled at –78 ºC. After 30 min of stirring, *tert*-butyldimethylsilyloxy trifluoromethanesulfonate (0.65 mL, 2.88 mmol) was added and the mixture was stirred for an additional 1 h. Then, the mixture was poured into pentane, the combined organic layers washed with water and brine and finally dried over Na_2SO_4. The residue obtained after evaporating the solvent was purified by column chromatography, using 8:2 hexane-ethyl acetate containing a small amount of Et_3N (2%), to afford 641 mg of the *enol silyl ether* **7** (83%) as a colourless oil. $[\alpha]_D^{28}$ -0.61º (6.56, $CHCl_3$); IR (film) 2949, 2859, 1704, 1580, 1249, 887 cm^{-1}; ^{1}H-NMR (300 MHz) δ 5.72 (1H, ddq, *J* 5; 3; 1.5 Hz, H-4), 4.72 (2H, s, H-2'), 3.69 (3H, s, CO_2Me), 3.41 (1H, d br, *J* 8.8 Hz H-6), 2.44 (1H, dddd, *J* 17.3, 9.2, 2.8, 2.8 Hz, H-5α), 2.28 (1H, ddd, *J* 17.3, 6.6, 0.7 Hz, H-5β), 1.79 (3H, br s, Me-C_3) 1.72 (3H, s, Me-$C_{1'}$), 0.99 (9H, s, *t*-Bu), 0.10 (3H, s, MeSi) and 0.08 (3H, s, MeSi) ppm; ^{13}C-NMR δ 168.5 (CO_2Me), 157.2 (C_1), 144.4 ($C_{1'}$), 132.9 (C_3), 127.6 (C_4), 110.9 (C_2), 110.9 ($C_{2'}$), 51.0 (CO_2Me), 40.2 (C_6), 27.2 (C_5), 25.6 (Me_3C), 21.3 (Me-C_3), 18.4 (Me_3C), 17.5 (Me-$C_{1'}$) -4.35 and -4.5 (Me_2Si) ppm; MS (EI) *m/z* 322 (M^+, 0.1), 307 (4), 281 (1), 265 (100), 235 (2), 223 (5), 233 (9). HRMS calculated for $C_{18}H_{30}O_3Si$ 322.1964, found 322.1967.

(1S,2S,5S,7S)-13-(tert-Butyldimethylsilanyloxy)-1,4-dimethyltricyclo[3.2.1.0^{2,7}]oct-3-ene-2-carboxylic acid methyl ester (**8**). A solution of diene **7** (641 mg, 1.99 mmol) in anhydrous toluene (10 mL) was transferred to a previously silylated ampoule and rigorously degassed by the freeze-thaw-cycle. The ampoule was cooled down under argon, a drop of propylene oxide was added and it was then sealed

under vacuum. After heating at 190 ºC for 48 h, the solvent was eliminated on a rotary evaporator and the residue was chromatographed, using 9:1 hexanes-ethyl acetate as eluent, to give 508 mg (80 %) of the *Diels-Alder adduct* **8** as a yellowish oil. $[\alpha]_D^{28}$ +26.2º (0.305, $CHCl_3$); IR (film) 2929, 2856, 1727, 1669 cm^{-1}; ^{1}H-NMR δ 3.73 (3H, s, CO_2*Me*), 2.27 (1H, dd, *J* 3.6, 3.6 Hz, H-5), 1.94 (1H, s br, H-7), 1.68 (1H, ddd, *J* 8.7, 3.5, 1.9 Hz, H-6β), 1.65 (3H, s br, Me-C_4), 1.41 (1H, dd, *J* 8.8, 3.6 Hz, H-8α), 1.24 (3H, s, Me-C_1) 1.08 (1H, d, *J* 8.7 Hz, H-8β), 0.92 (1H, d br, *J* 8.7 Hz, H-6α), 0.98 (9H, s, *t*-Bu), 0.05 (3H, s, MeSi), 0.00 (3H, s, MeSi) ppm; ^{13}C-NMR δ 170.5 (*C*O_2Me), 136.6 (C_4), 114.8 (C_3), 51.8 (CO_2*Me*), 37.3 (C_2), 37.0 (C_5), 35.5 (C_6), 31.3 (C_1), 30.1 (C_8), 26.9 (C_7), 25.7 (*Me*$_3$C), 18.05 (Me$_3$*C*), 15.5 (Me-C_1), 14.55 (Me-C_4), -4.05 y -4.28 (*Me*$_2$Si) ppm; MS (EI) *m/z* 322 (M^+, 0.4), 307 (3), 291 (3), 266 (25, 265 (100), 210 (2). HRMS calculated for $C_{18}H_{30}O_3Si$ 322.1964, found 322.1953.

(6S)-2-[(tert-Butyldimethylsilanyl)methoxy]-6-[1-(diphenylvinylsilanyloxymethyl)vinyl]-3-methylcyclo- hexa-1,3-dienecarboxylic acid methyl ester (**13**). 10-Hydroxycarvone (**10**) was prepared from carvone as described in reference [16]; $[\alpha]_D^{22}$ -155º (c 3.4, $CHCl_3$); IR (NaCl) 3424, 2922, 2887, 1668, 1451, 1414, 1143, 902, 903 cm^{-1}; ^{1}H-NMR δ 6.75 (1H, ddq, *J* 5.8, 2.6, 1.3, H-3), 5.15 (1H, s, H-2'), 4.95 (1H, s, H´-2'), 4.15 (2H, s, CH_2OH), 2.82 (1H, dddd, *J* 18.3, 5.8, 4.3, 1.4, H-5), 2.61 (H, ddd, *J* 16.0, 3.7, 1.5, H-6α), 2.48 (1H, dddd, *J* 18.3, 5.8, 4.3, 1.4, H-4α), 2.39 (1H, dd, *J* 16.0, 13, H-6β), 2.32 (1-H, dddd, *J* 18.1, 10.6, 2.5, 2.6, H-4β), 1.78 (3H, s, CH_3-C_2) ppm. MS (EI) m/z, 166 (M^+, 13), 148 (67), 135 (17), 106 (63), 91 (42), 82 (100); HRMS calculated for $C_{10}H_{14}O_2$166.0994, found 166.1075.

Et_3N (0.72 mL, 5.16 mmol) and chloro(diphenyl)vinylsilane (0.7 mL, 3.17 mmol) were sequentially added to a solution of 10-hydroxycarvone (**10**, 360 mg, 2.16 mmol) in dry THF (8 mL) at -20ºC. After 1h the reaction mixture was treated with aqueous saturated solution of NH_4Cl and extracted with hexane. The combined organic extracts were washed with dilute HCl, 10% aqueous $NaHCO_3$ solution and brine and dried over Na_2SO_4. Evaporation of the solvent afforded an oily residue that was purified by column chromatography, using 8:2 hexane-ethyl acetate as eluent, to give 647 mg (80%) of *silyl ether* **11** as an oil; $[\alpha]_D^{22}$ -25º (c 0.65, $CHCl_3$); IR (NaCl) 3068, 2922, 1675, 1428, 1117, 711 cm^{-1}; ^{1}H-NMR δ 7.6 (5 H, m, H-Ar), 7.6 (5 H, m, H-Ar), 6.72 (1H, dddq, *J* 5.7, 2.6, 1.32 H-3), 6.60 (1H, dd, *J* 14.9, 20.16 H-1''), 6.28 (1H, dd, *J* 14.9, 3.9 H-2''), 5.91 (1H, dd, *J* 20.16, 3.9 H-2''), 5.2 (1H, s, H-2'), 4.90 (1H, s, H´-2'), 4.27 (2H, br s, H-3'), 2.76 (1H, dddd, J 17.71, 14.34, 3.5, 3.5 H-5), 2.60 (1H, ddd, J 16.2, 3.84, 1.51 H-6α), 2.36 (1H, dd, J 16.2, 13.68 H-6β), 2.43 (1H, m, H-4), 2.25 (1H, m, H-4'), 1.78 (3H, s, CH_3-C_2) ppm; ^{13}C-NMR δ 199.53 (C_1), 149.22 ($C_{1'}$), 144.49 (C_3), 135.41 (C_2), 134.94 (C_{Ar}), 137.30 ($C_{2''}$), 133.78 (C_{Ar}), 133.09 ($C_{1''}$), 130.13 (C_{Ar}), 127.90 (C_{Ar}), 110.12 ($C_{2'}$), 65.30 ($C_{3'}$), 43.62 (C_6), 37.96 (C_5), 32.00 (C_4), 15.68 (Me-C_2); MS (EI) m/z, 374 (M^+, 6), 347 (15), 297 (43), 283 (30), 209 (100); HRMS calculated for $C_{24}H_{26}O_2Si$ 374.1702, found 374.1708.

A solution of compound **11** (200 mg, 0.56 mmol) in THF (2 mL) was added dropwise to a solution of LDA in THF (1.2 mL of a 0.5M solution, 0.60 mmol) at -78 ºC. The reaction mixture was allowed to warm to 0 ºC (*ca*. 2 h) and stirred at this temperature for 30 min, cooled to -78 ºC, and treated with methyl cyanoformate (57 μL, 0.71 mmol). After 30 min the reaction mixture was allowed to warm to

room temperature, poured into saturated NH_4Cl solution and extracted with ether. The combined organic layers were washed with brine and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was purified by column chromatography, using 9:1 hexane-ethyl acetate as eluent, to give 200 mg (82%) of *β-keto ester* **12** as an oil; $[\alpha]_D^{22}$ -47º (c 0.3, $CHCl_3$); IR (NaCl) 3180, 2923, 1745, 1674, 1155, 1117, 711cm^{-1}; ^{1}H-NMR δ 7.6 (5 H, m, H-Ar), 7.6 (5 H, m, H-Ar), 6.73 (1H, m, H-4), 6.45 (1H, dd, *J* 14.9, 19.2 H-1''), 6.30 (1H, dd, *J* 14.9, 4.0 H-2''), 5.91 (1H, dd, *J* 19.2, 4.0 H-2''), 5.29 (1H, s, H-2'), 5.05 (1H, s, H´-2'), 4.27 (1H, s, H3'), 3.67 (3H, s, CO_2Me), 3.55 (1H, d, *J* 6.97 Hz, H-1), 3.10 (1H, ddd, *J* 10.74, 12.81, 4.71 H-6), 2.50 (1H, dddd, *J* 18.9, 10.74, 4.71, 1.32 H-5α), 2.30 (1H, dddd, *J* 18.9, 10.7, 2,5, 2,5 H-5β), 1.79 (3H, s, CH_3-C_3) ppm; ^{13}C-NMR δ 194.73 (C_2), 170.08 (CO_2Me), 147.90 ($C_{1'}$), 144.43 (C_4), 135.68 (C_3), 134.92 (C_{Ar}), 137.28 ($C_{2''}$), 133.72 (C_{Ar}), 133.01 ($C_{1''}$), 130.12 (C_{Ar}), 127.90 (C_{Ar}), 111.52 ($C_{2'}$), 65.51 ($C_{3'}$), 58.82 (C_1), 51.98 (CO_2Me), 40.97 (C_6), 32.14 (C_5), 15.71 (Me-C_3); MS (EI) *m/z,* 432 (M^+, 6), 405 (23), 355 (100), 323 (15), 208 (79), 183 (71); HRMS calculated for $C_{26}H_{28}O_4Si$ 432,1756, found 432,1729.

A solution of enone **12** (70 mg, 0.18 mmol) in dry CH_2Cl_2 (0.7 mL) was cooled to -78 ºC and treated sequentially with 0.5M solution of lithium *bis*(trimethyl)silylamide in hexane (0.5 mL, 0.25 mmol) and *tert*-butyldimethylsilyl triflate (0.07 mL, 0.23 mmol). After 1 h at -78 ºC, the reaction mixture was poured into pentane and washed with cool water and brine, before being dried over Na_2SO_4. Evaporation of the solvent under vacuum furnished an oily residue which was purified by column chromatography on silica gel, using hexane-ethyl acetate 8:2 with a 1% of Et_3N as eluent, to give 75 mg of the *enol silyl ether* **13** as a colourless oil (83%); $[\alpha]_D^{28}$ -46.6º (0.3, $CHCl_3$); IR (NaCl) 3120, 2949, 1704, 1578, 1430, 1360, 1173, 1118, 886, 841 cm^{-1}; ^{1}H-NMR (C_6D_6) δ 7.6 (5 H, m, H-Ar), 7.6 (5 H, m, H-Ar), 6.42 (1H, dd, *J* =15.0, 20.16, H-1''), 6.15 (1H, dd, *J*= 15.0, 3.9, H-2''), 5.85 (1H, dd, *J* =20.16, 3.9, H-2''), 5.28 (1H, br s, H-4), 5.28 (1H, br s, H-2'), 5.10 (1H, br s, H-2'), 4.2 (2H, br s, -CH_2O-), 3.62 (1H, br d, *J*= 8.0 Hz, H-6), 3.32 (3H, s, CO_2Me), 2.20 (1H, dddd, *J* 17.3, 9.2, 2.8, 2.8 Hz, H-5α), 1.19 (1H, ddd, *J* =17.3, 6.6, 0.7 Hz, H-5β), 1.65 (3H, br s, Me-C_3) 1.04 (9H, s, *t*-Bu), 0.15 (3H, s, MeSi) and -0.03 (3H, s, MeSi) ppm; ^{13}C-NMR δ 167.23 (CO_2Me), 157.7 (C_1), 147.1 ($C_{1'}$), 136.9 ($C_{2''}$), 135.5 (C_{Ar}), 134.0 (C_{Ar}), 133.26 (C_3), 130.2 ($C_{1''}$), 128.4 (C_{Ar}), 128.2 (C_{Ar}), 127.9 (C_4), 110.9 (C_2), 110.6 ($C_{2'}$), 65.7 (CH_2O), 50.1 (CO_2Me), 36.6 (C_6), 27.9 (C_5), 25.9 (Me_3C), 18.7 (Me-C_3), 17.8 (Me_3C), -3.4 and –3.1 (Me_2Si) ppm; MS (EI) *m/z* 546 (M^+, 3), 531 (10), 489 (83), 461 (14), 231 (100); HRMS calculated for $C_{32}H_{42}O_4Si_2$ 546.2622, found 546.2636.

(1S,2S,5R,7S)-3-(tert-Butyldimethylsilanyloxy)-1-(diphenylvinylsilanyloxymethyl)-4-methyltricyclo-[3.2.1.0^{2,7}]oct-3-ene-2-carboxylic acid methyl ester (**14**). A solution of diene **13 (**20 mg, 0.04 mmol) in anhydrous toluene (2 mL) was transferred to a previously silylated ampoule and degassed by the freeze-thaw-cycle. The ampoule was cooled down under argon, a drop of propylene oxide was added and it was then sealed. After heating at 190 ºC for 48 h, the solvent was eliminated under vacuum and the residue was chromatographed, using 9:1 hexane-ethyl acetate as eluent, to give 18.5 mg (92 %) of the *Diels-Alder adduct* **14** as an oil; ^{1}H-NMR δ 7.6 (5 H, m, H-Ar), 7.6 (5 H, m, H-Ar), 6.45 (1H, dd, *J* 15.0, 20.16 H-1''), 6.25 (1H, dd, *J* 15.0, 3.9 H-2''), 5.84 (1H, dd, *J* 20.16, 3.9 H-2''), 3.58 (3H, s,

CO_2Me), 2.30 (1H, dd, *J* 4.5, 4.5 Hz, H-5), 2.4 (1H, br s, H-7), 1.68 (1H, ddd, *J* 12, 4.5, 2.4 Hz, H-8β), 1.65 (3H, br s, Me-C_4), 1.72 (1H, dd, *J* 11, 6 Hz, H-6α), 1.05 (1H, d, *J* 11 Hz, H-6β), 0.91 (1H, H-8α), 0.93 (9H, s, t-Bu), -0.05 (3H, s, MeSi), -0.06 (3H, s, MeSi) ppm. ^{13}C-NMR δ 170.1 (CO_2Me), 137.9 ($C_{2'}$), 136.8 (C_4), 135.8 (C_{Ar}), 134.1 ($C_{1'}$), 134.0 (C_{Ar}), 130.6 (C_{Ar}), 128.7 (C_{Ar}), 115.4 (C_3), 63.8 (CH_2O), 52.6 (OMe), 37.5 (C_5), 37.2 (C_2), 36.4 (C_1), 32.0 (C_6), 30.5 (C_8), 26.6 (*Me*$_3$C), 26.2 (C_7), 18.1 (Me$_3$*C*), 16.5 (Me-C_3), -4.0 and 4.1 (Me_2Si).

(1S,2R,4S,5R)-4-(tert-Butyldimethylsilanyloxy)-1,4-dimethyl-3-oxo-tricyclo[3.2.1.0^{2,7}]octane-2-carboxylic acid methyl ester (**15**). *m*-Chloroperbenzoic acid (1.71 g, 9.92 mmol) was added to a solution of silyl enol ether **8** (800 mg, 2.48 mmol) in dichloromethane (30 mL) at –30 ºC. The reaction mixture was stirred for 2 ½ h and then poured into ethyl acetate, washed with water and brine and dried over Na_2SO_4. The residue left after vacuum evaporation of the solvent was purified by chromatography, using 9:1 hexanes-ethyl acetate as eluent, to afford the *silyl ether-ketone* **15** (770 mg, 92 %) as a solid; mp 118.5-120.0 ºC (from methanol); $[\alpha]_D^{28}$ +31.06º (0.515, $CHCl_3$); IR (KBr) 2953, 1734, 1704, 1252, 833 cm^{-1}; ^{1}H-NMR (300 MHz) δ 3.75 (3H, s, CO_2*Me*), 2.34 (1H, d br, *J* 2.8 Hz, H-7), 2.39 (1H, d, *J* 12.6 Hz, H-8β), 2.05 (1H, dd, *J* 4.9, 4.7 Hz, H-5), 1.98 (1H, ddd, *J* 13,5.5, 3.2 Hz, H-6β), 1.85 (1H, d, *J* 12.8 Hz, H-6α), 1.66 (1H, dd, *J* 12.8, 5.1 Hz, H-8α), 1.29 (3H, s, Me-C_1) 1.19 (3H, s br, Me-C_4), 0.85 (9H, s, *t*-Bu), 0.19 (3H, s, MeSi), 0.04 (3H, s, MeSi) ppm; ^{13}C-NMR δ 203.3 (C_3), 168.2 (*C*O_2Me), 75.2 (C4), 52.3 (CO_2*Me*), 47.0 (C_2), 42.5 (C_5), 38.45 (C_1), 35.8 (C_7), 33.2 (C_8), 29.1 (C_6), 25.7 (*Me*$_3$C), 22.6 (Me-C_4),18.3 (Me$_3$*C*), 16.4 (Me-C_1), -2.8 y -3.7 (*Me*$_2$Si) ppm; MS (EI) *m/z* 338 (M^+, 0.1), 281 (67), 249 (36), 175 (10), 155 (95), 138 (100); HRMS calculated for $C_{18}H_{30}O_4Si$ 338.1913, found 338.1926.

(1S,4S,5S,7R)-4-(tert-Butyldimethylsilanyloxy)-3-hydroxy-4,7-dimethylbicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl ester (**16**). Silyl ether **15** (100 mg, 0.29 mmol) was dissolved under argon in a 9:1 mixture of THF/*tert*-butanol (1.2 mL). The mixture was cooled to –40 ºC and a 0.5 M solution of SmI_2 in THF was added dropwise until persistence of the blue colour. The reaction mixture was poured into hexane and the organic layer was washed with water, 5% aqueous $Na_2S_2O_4$ solution and brine and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was chromatographed, using 9:1 hexane-ethyl acetate as eluent, to give the *cyclopropane cleavage product* **16** (80 mg, 80 %) as an oil; IR (film) 2954, 2828, 1726, 1650, 1608, 1262, 836 cm^{-1}; ^{1}H-NMR (400 MHz) δ 3.74 (3H, s, CO_2*Me*), 2.75 (1H, dd, *J* 4.8, 4.4 Hz, H-1), 2.11 (1H, dd, *J* 6.8, 5.6 Hz, H-5), 1.78 (1H, dd, *J* 14, 10.4, 7.6 Hz, H-6α), 1.73 (1H, d, *J* 9.2 Hz, H-8α), 1.62-1.55 (2H, m, H-8β and H-6β), 1.46 (3H, br s, Me-C_4), 0.84 (3H, d, *J* 6.8 Hz, Me-C_7), 0.86 (9H, s, *t*-Bu), 0.16 (3H, s, MeSi), 0.08 (3H, s, MeSi) ppm;^{13}C-NMR (75 MHz) δ 173.3 (*C*O_2Me), 173.1 (C_3), 100.1 (C_2), 78.4 (C_4), 51.4 (CO_2*Me*), 48.3 (C_5), 39.2 (C_7), 38.2 (C_1), 36.7 (C_6), 31.3 (C_8), 27.05 (Me-C_4), 25.9 (*Me*$_3$C), 18.6 (Me$_3$*C*),16.7 (Me-C_7), -2.54 y -2.88 (*Me*$_2$Si) ppm; MS (EI) *m/z* 340 (M^+, 0.0), 339 (0.1), 281 (45), 251 (100), 175 (3), 75 (22); HRMS calculated for $C_{18}H_{32}O_4Si$ 340.2070, found 340.2071.

(1R,4S,5R,7S)-4-(tert-Butyldimethylsilanyloxy)-3-hydroxy-7-methoxy-4,7-dimethyl-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl ester (**18**). Concentrated HCl (0.15 mL) was added to a solution of compound **15** (50 mg, 0.15 mmol) in CH_3OH (4 mL). After stirring for 6 h, the mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were successively washed with a saturated aqueous solution of $NaHCO_3$, water and brine and dried over Na_2SO_4. The solvent was evaporated under vacuum and the residue was chromatographed on silica gel, using 9:1 hexane-ethyl acetate as eluent, to give 42 mg of *methyl ether* **17** (76%) as an oil; $[\alpha]_D^{28}$ +18.96º (1.16, $CHCl_3$); IR (film) 3429, 2924, 1649, 1600, 1219, 829 cm^{-1}; ^{1}H-NMR (300 MHz) δ 3.77 (3H, s, CO_2*Me*), 3.19 (3H, s, O*Me*), 2.88 (1H, d *J* 4.1 Hz, H-1), 2.18 (1H, dd, *J* 6.2, 6.6 Hz, H-5), 2.11-2.04 (2H, m, H-8β and H-6β), 1.76 (1H, dd, *J* 14.9, 7.5 Hz, H-6α), 1.59 (1H, d, *J* 11.01 Hz, H-8α), 1.47 (3H, br. s, Me-C_4), 1.16 (3H, s, Me-C_7), 0.86 (9H, s, *t*-Bu), 0.19 (3H, s, MeSi), 0.07 (3H, s, MeSi) ppm; ^{13}C-NMR δ 173.1 (*C*O_2Me), 172.8 (C_3), 101.3 (C_2), 87.4 (C_7), 77.00 (C_4), 51.65 (CO_2*Me*), 49.8 (OMe), 47.7 (C_5), 40.9 (C_1), 37.6 (C_6), 33.65 (C_8), 26.7 (Me-C_4), 25.9 (*Me*$_3$C), 18.9 (Me-C_7), 18.6 (Me$_3$*C*), -2.5 and -3.3 (*Me*$_2$Si) ppm.

(1R,4S,5R,7S)-7-Benzyloxy-4-(tert-butyldimethylsilanyloxy)-3-hydroxy-4,7-dimethylbicyclo [3.2.1]-oct- 2-ene-2-carboxylic acid methyl ester (**19**). A mixture of **15** (60 mg, 0.18 mmol), benzyl alcohol (0.092 mL, 0.88 mmol) and PTSA (3 mg, 5%) in CH_2Cl_2 (1 mL) was stirred at room temperature for 6h. The reaction mixture was poured into an aqueous saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification by column chromatography, using 8:2 hexane-ethyl acetate, afforded 61.0 mg (80%) of compound **19** as an oil; $[\alpha]_D^{28}$ +20º (1.3, $CHCl_3$); ^{1}H-NMR (300 MHz) δ 12.18 (1H, s, HO), 7.36-7.29 (5H, m, Ph), 3.79 (3H, s, CO_2*Me*), 4.46 (1H, d AB system, *J* 11.7 Hz, CH_2O), 4.42 (1H, d AB system, *J* 11.5 Hz, CH_2O), 3.00 (1H, dd *J* 2.5, 2.5 Hz, H-1), 2.24-2.16 (3H, m, H-5, H-6β and H-8β), 1.90 (1H, dd, *J* 14.8, 7.2 Hz, H-6α), 1.64 (1H, d, *J* 11.6 Hz, H-8α), 1.48 (3H, br s, Me-C_4), 1.30 (3H, s, Me-C_7), 0.86 (9H, s, t-Bu), 0.165 (3H, s, MeSi), 0.08 (3H, s, MeSi) ppm; ^{13}C-NMR (75 MHz) δ 173.2 (CO_2Me), 172.85 (C_3), 139.7 ($C_{1'}$), 128.3 and 127.2 ($C_{2'}$-$C_{6'}$ and $C_{3'}$-$C_{5'}$), 127.1 ($C_{4'}$)101.2 (C_2), 87.9 (C_7), 77.2 (C_4), 64.6 (CH_2O) 51.7 (CO_2*Me*), 47.8 (C_5), 41.4 (C_1), 38.2 (C_6), 33.8 (C_8), 26.7 (Me-C_4), 25.7 (*Me*$_3$C), 19.8 (Me-C_1), 18.6 (Me$_3$*C*), -2.5 and -2.8 (Me_2Si) ppm; MS (EI) m/z 432 (M^+, 0.2), 389 (60), 357 (100), 223 (47), 191 (39); HRMS $C_{25}H_{38}O_5Si$ requires 446.2488, found 446.2485.

(1R,4S,5R,7S)-4-(tert-Butyldimethylsilanyloxy)-3,7-dihydroxy-4,7-dimethyl-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl ester (**20**). Concentrated HCl (0.1 mL) was added to a solution of **15** (35 mg, 0.1036 mmol) in a 1:1 mixture of THF-H_2O (2 mL). The mixture was stirred at room temperature overnight, then diluted with ethyl acetate and washed successively with 10% aqueous solution of $NaHCO_3$, water and brine. Drying over Na_2SO_4 and evaporation of the solvent afforded 29 mg (80%) of crude *alcohol* **20**, which by ^{1}H-NMR appeared to be quite pure. The alcohol **20** was an amorphous solid that could not be induced to crystallize, nor could it be purified by column chromatography due

to its propensity to give **15**. ^{1}H-NMR δ 3.72 (3H, s, CO_2Me), 3.05 (1H, dd *J* 3.7, 3.7 Hz, H-1), 1.53 (3H, s, Me-C_7), 1.41 (3H, br s, Me-C_4) 0.82 (9H, s, t-Bu), 0.10 (3H, s, MeSi), 0.02 (3H, s, MeSi) ppm; ^{13}C-NMR δ 173.42 (CO_2Me), 171.24 (C_3), 101.45 (C_2), 84.50 (C_7), 77.52 (C_4), 51.82 (CO_2Me), 48.07 (C_5), 47.55 (C_1), 42.95 (C_6), 33.93 (C_8), 28.05 (Me-C_4), 26.84 (Me-C_7) 25.83 (Me_3C), 18.43 (Me_3C), -2.55 and -2.39 (Me_2Si) ppm.

(1R,4S,5R,7S)-4-(tert-Butyldimethylsilanyloxy)-7-chloro-3-hydroxy-4,7-dimethylbicyclo[3.2.1]oct-2-ene- 2-carboxylic acid methyl ester (**21**). Concentrated HCl (0.7 mL) was added to a solution of compound **15** (20 mg, 0.06 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 2h, diluted with ethyl acetate and successively washed with 10% aqueous solution of $NaHCO_3$, water and brine. Drying over Na_2SO_4 and evaporation of the solvent afforded 19 mg (86%) of crude *chloride* **21** as an oil; ^{1}H-NMR (300 MHz) δ 12.06 (1H, s, OH), 3.77 (3H, s, CO_2Me), 2.67 (1H, dd J 3.8, 3.8 Hz, H-1), 1.47 (3H, br s, Me-C_4), 1.27 (3H, s, Me-C_7), 0.86 (9H, s, *t*-Bu), 0.15 (3H, s, MeSi), 0.06 (3H, s, MeSi) ppm; ^{13}C-NMR (75 MHz) δ 172.81 (CO_2Me), 171.24 (C_3), 101.39 (C_2), 53.3 (C_7), 77.52 (C_4), 51.64 (CO_2Me), 47.96 (C_5), 45.57 (C_1), 42.95 (C_8), 34.6 (C_6), 26.77 (Me-C_4), 25.22 (Me-C_7) 25.83 (Me_3C), 18.56 (Me_3C), -2.52 y -2.87 (Me_2Si) ppm.

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Sample Availability: The following compounds and amounts are available from the authors: compound **4**, 15 mg; compound **8**, 20 mg; compound **15**, 15 mg; compound **16**, 10 mg; compound **17**, 10 mg; compound **18**, 30 mg.