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Enantioselective Synthetic Methodology to Prepare *trans*-Fused Bicyclo[5.3.0]decane Systems: an Approach to the Synthesis of the Pseudoguaiane Carbon Framework

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Abstract—An enantioselective method to prepare *trans*-fused bicyclo[5.3.0]decane systems is described. This methodology is based on two key reactions: a [4+3] cycloaddition reaction (to generate the seven-membered ring) and the Nicholas reaction (to insert the five-membered ring). The application of this methodology to the enantioselective synthesis of the pseudoguaiane carbon skeleton is presented. This enantioselective strategy for construction of the *trans*-fused bicyclo[5.3.0]decane system is versatile and could be applied to the preparation of a wide range of bioactive natural products containing that carbon framework.

The 5,7-fused ring system is found in many natural products.[1] In recent reviews on sesquiterpenes it is stated that of several hundreds new sesquiterpenes isolated from natural sources, about 100 possess the 5,7-fused ring framework,[1a,b] most of them with important biological activity.[2] The availability of methodologies to efficiently synthesize polycyclic, multifunctional systems, in an enantioselective manner, is of great interest in synthetic chemistry. Our major interest and objective was to develop a strategy which would assemble the *trans*-fused bicyclo[5.3.0] ring system in an early step of a synthetic pathway and that would be sufficiently versatile to allow further transformations and functionalization within the rings and/or at the substituents.

According to the literature, the major strategy employed for the construction of the bicyclo[5.3.0] carbon framework[3] was the annulation of either the cyclopentane ring or the cycloheptane ring. The transannular cyclization of appropriately built and functionalized cyclodecanes, and the rearrangements of either bicyclo[4.3.1]decanes or hydronaphthalenes are other strategies to synthesize the 5,7-fused ring system. Few of the aforementioned methods give the *trans*-fused bicyclo[5.3.0]system[4] and even less construct the requisite ring system in an enantioselective manner.[5]

We have developed a synthetic methodology to construct *trans*-fused bicyclo[5.3.0]decane carbon skeletons, conveniently functionalized and in an enantioselective manner. We report here the application of this synthetic strategy to the enantioselective synthesis of the sesquiterpenic pseudoguaiane carbon skeleton, which is the framework of pseudoguaianolides, a large family of very important bioactive natural products (with important biological activities such as: antitumour, antileukemic, anti-inflammatory, antifungal, antihelminthic, moluscicide, allergenic, etc.).[2a–f] It is a methodology based on two key reactions: a [4+3] cycloaddition reaction[6] (to generate the seven-membered ring, see Scheme 1) and the Nicholas reaction[7] (to electrophilically insert the propargylic C3-entity which will, in turn, facilitate the construction of the five-membered ring by intramolecular cyclization, see Scheme 2).

Moreover, it is a versatile synthetic strategy, because by choosing an adequate substitution pattern in the propargylic, furan and dihaloketone (for preparation of the 2-oxyallyl cation) precursors it is possible to prepare a wide range of related structures.[8] An active effort in this research field has been carried out in our laboratory.

The cycloheptane moiety of our bicyclic system is prepared by a [4C(4π)+3C(2π)] cycloaddition reaction between furan and 1,3-dimethyl-2-oxyallyl cation (Scheme 1), generated in situ by reduction of 2,4-dibromo-3-pentanone **1** with Cu/NaI at 55°C.[9] This reaction afforded a mixture of diastereoisomers **2a**/**2b** in an 80:20 ratio and in 92% yield[8b–d] (Scheme 3).

Keywords: bicyclo[5.3.0]decane; pseudoguaiane; [4+3]-cycloaddition; Nicholas reaction; enantioselective synthesis.
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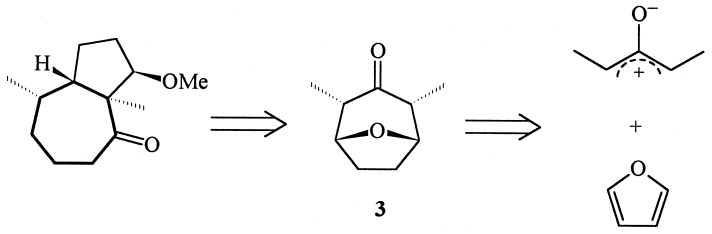


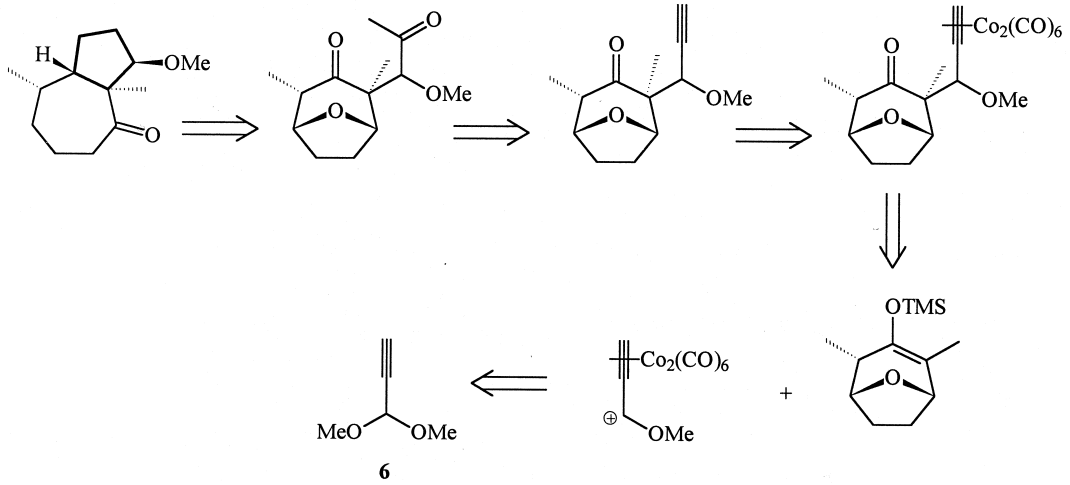
Scheme 1. Retrosynthesis of the seven-membered ring of the bicyclo[5.3.0]decane system.

The major diastereoisomer **2a** has both methyl groups in diequatorial disposition for a boat-like conformation of the 1-oxan-4-one ring, and it is easily separable from **2b** by column chromatography. Haloketone **1** was obtained in 71% yield by bromination of cheap and commercially available 3-pentanone under acidic catalysis.[9] Catalytic hydrogenation of the C6–C7 double bond afforded in 94% yield the oxabicyclic compound **3**.

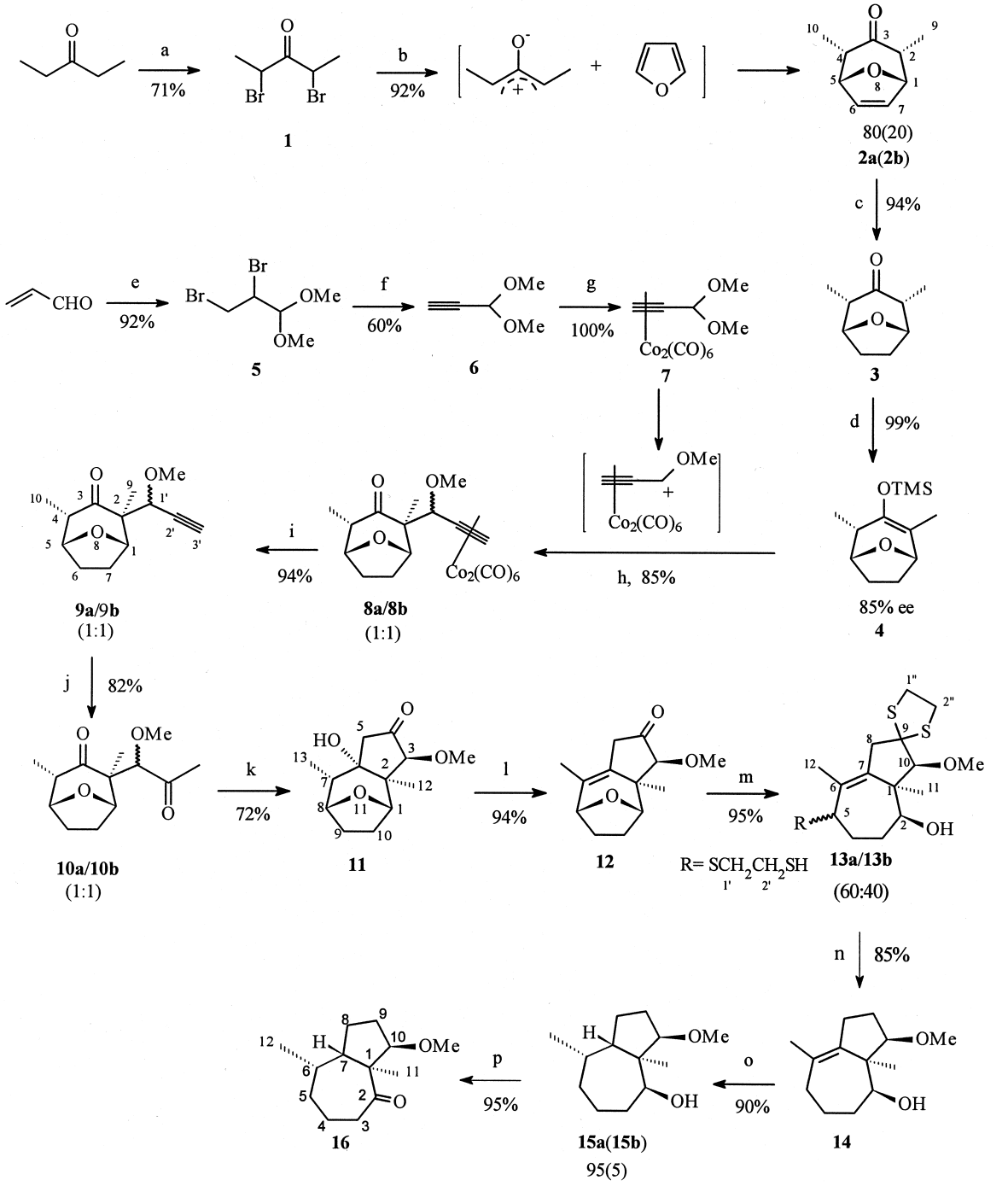
The optically inactive oxabicycle **3** is efficiently converted into the enantiomerically enriched silyl enol ether **4**, in 99% yield and 85% ee (see Experimental for details of ee determination), by its treatment at −78°C with lithium (*S*,*S*′)-1,1′-dimethylbenzylamide,[10,11] in the presence of lithium chloride.[12] This chiral base is commercially available[13] in both enantiomeric forms but also could be efficiently prepared[14] by condensation of acetophenone with (*S*)-1-phenylethylamine followed by hydrogenation of the resulting imine. This chirality induction is quite efficient because: (a) It affords a good ee, whose optimization and improvement is under study in our laboratory; (b) It is carried out in an early step in the synthetic pathway, which has an economical advantage; (c) The precursor **3** is a *meso* form which does not have any problem of chemioselectivity or regiochemistry in the attack of lithium amide; (d) The chiral base can be recovered in 95% yield (by extracting an ethereal solution of the crude reaction mixture containing it, with aq. HCl 0.1 M at 0°C), without affecting silyl enol ether **4**. Thus, the chiral base recovered as amine hydrochloride could be recrystallized, if necessary, and converted into the amine by treatment with aq. NaOH and reused; (e) The availability of both enantiomers of the chiral base allows the preparation of both enantiomers of the silyl enol ether.

The three-carbon subunit, necessary to assemble the five-membered ring of the bicyclo [5.3.0] system, is introduced by electrophilic attack of methoxypropargylic cation (stabilized as a dicobalt hexacarbonyl complex) on silyl enol ether **4** (Nicholas reaction). This propargylic cation is generated in situ from cobalt complex **7** by treatment with $BF_3{\cdot}OEt_2$.[4a,15] Compound **7** is prepared in 55% overall yield starting from acrolein[9,16] (see Scheme 3). The Nicholas propargylation of **4** produced in 75% yield a 1:1 diastereoisomeric mixture of **8a**/**8b**, epimers at C-1′. The ratio between both epimers may vary with reaction conditions (temperature and reaction time) but both of them are useful for our synthetic purposes as explained below. In this reaction two stereocentres were generated, thus four diastereoisomers could be theoretically formed. However, due to the bulkiness of the organocobalt cluster, the attack of propargylium cation is only possible on the *exo* face of silyl enol ether **4** forming only two diastereoisomers (see Fig. 1).

Compounds **8a** and **8b** were separated by column chromatography for their physical and spectroscopic characterization, but for synthetic purposes both of them were reacted as a mixture. The establishment of the relative configuration in **8a** and **8b** was carried out by a ^1H and ^{13}C NMR comparative correlation study and NOE experiments.[17]



Scheme 2. Retrosynthetic analysis of the five-membered ring generation by the Nicholas reaction.



Scheme 3. Synthetic pathway to prepare *trans*-bicyclo[5.3.0]decane synthon, precursor of pseudoguaiane carbon framework: (a) Br_2 (2 equiv.), PBr_3 (cat.), 0°C; (b) Furan, NaI, Cu, 55°C, chromatographic separation; (c) H_2, Pd/C(10%), EtOH, rt; (d) (*S*,*S*′)-1,1′-dimethyldibenzylamine, BuLi, LiCl, −78°C, then TMSCl; (e) Br_2, then $HC(OMe)_3$, MeOH; (f) $[Bu_4N]OH$; (g) $Co_2(CO)_8$, pentane, rt; (h) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0°C; (i) CAN, Et_3N, acetone, 0°C; (j) Hg(II) *p*-toluensulfamidate, $EtOH/H_2O$ (85:15), reflux; (k) Anh. KOH, abs. EtOH, rt; (l) $SOCl_2$, Py, −24°C; (m) $HSCH_2CH_2SH$, $BF_3{\cdot}OEt_2$, 0°C; (n) Raney-Ni, EtOH, reflux; (o) H_2, Pd/C(10%), anh. MeOH, rt, chromatographic separation; (p) PCC, CH_2Cl_2, rt.

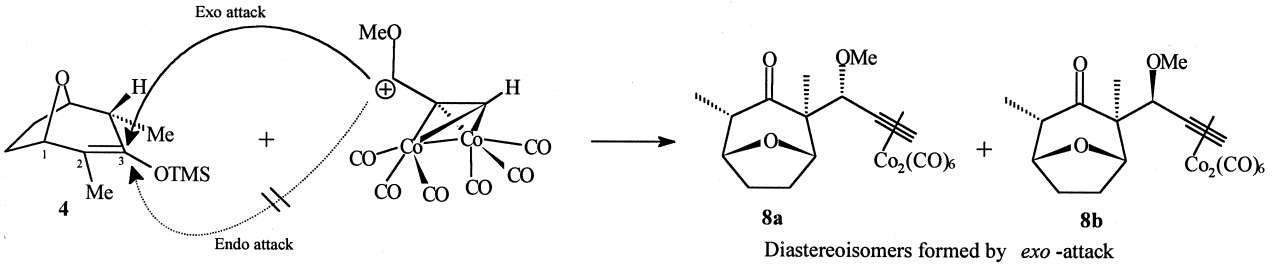


Figure 1. Preferential attack of the cobaltcarbonyl propargylium cation on the *exo* face of the π-system of silyl enol ether **4**.

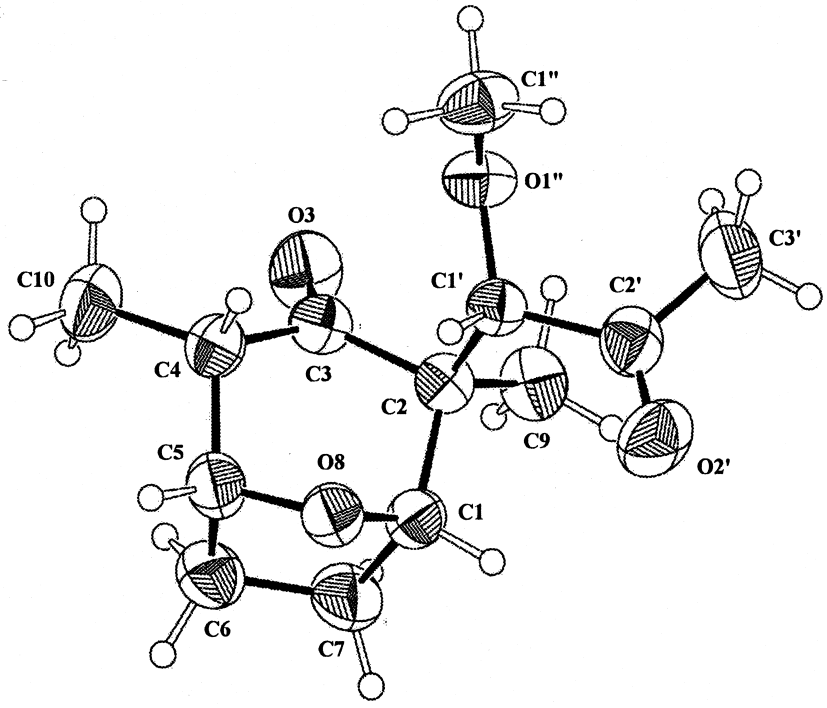


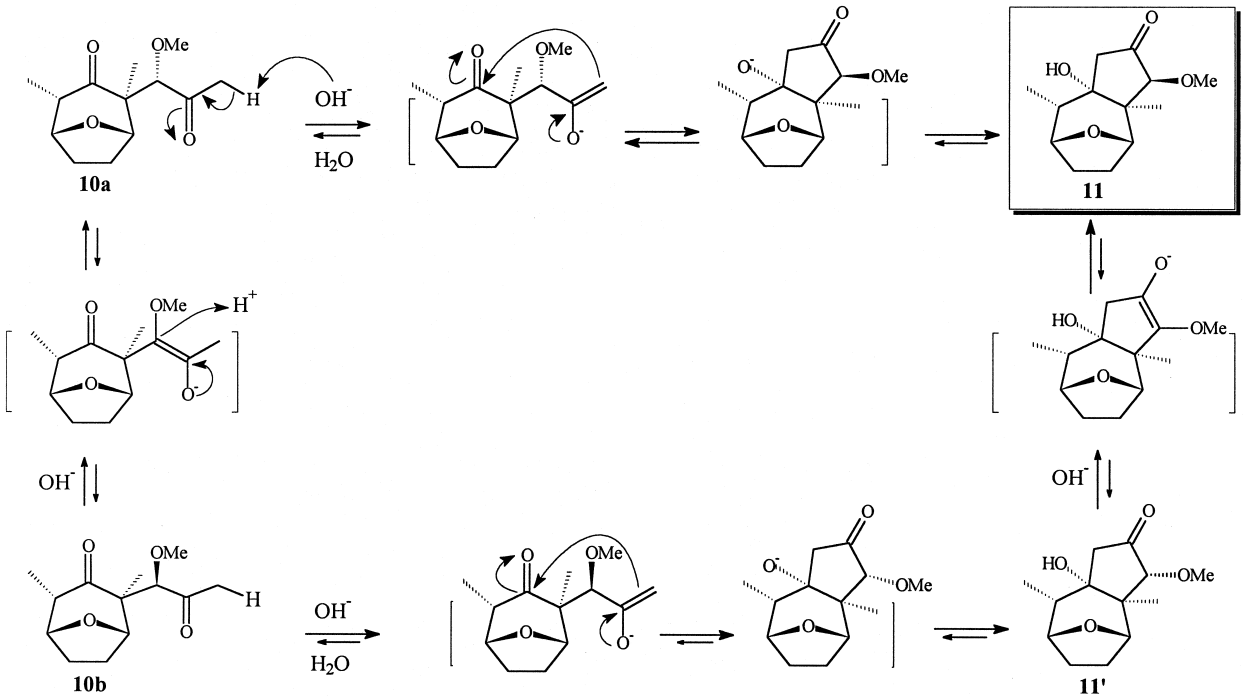
Figure 2. X-Ray structure of **10a**. Thermal ellipsoids are shown at 50% level.

The mixture of cobalt complexes **8a**/**8b** was demetallated with cerium(IV) ammonium nitrate (CAN) and NEt_3 in acetone as a solvent affording acetylenes **9a**/**9b** in 94% yield. Under these conditions both epimers are configurationally stable and the ratio **9a**:**9b**=1:1 is identical to that of the precursors. In the next step, epimers **9a** and **9b** were reacted as a mixture but for their characterization were also separated and purified by column chromatography. If Nicholas coupling and demetallation are carried out in one pot the overall yield of both steps could be improved by up to 10%.[15]

Hydration of a triple bond is usually carried out by using H_2SO_4/H_2O/AcOH systems in the presence of Hg(II) salts.[18] These reaction conditions afforded in our case a low yield of products and propitiated polymerization of acetylenes and epimerization of stereocentres, via enolization of ketones, among other side processes. To avoid this problem, hydration of the triple bond was performed under neutral conditions[4a,b] by using mercury(II) *p*-toluenesulfamidate[19] to give diketones **10a**/**10b** (1:1) in 82% yield. Under these conditions, molecules **10a** and **10b** were configurationally stable and no modification of stereocentres at C4 and C1′ was observed. This behaviour was confirmed by performing the hydration reaction on separated acetylenes **9a** and **9b**, obtaining in each case only one product **10a** and **10b**, respectively. By careful ^1H and ^{13}C NMR correlation studies, it was concluded that the stereocentre at C4 did not undergo epimerization during the hydration reaction. If that phenomenon had happened an important deshielding on the H_3–C10 signal would have been observed in the hypothetical epimerized compound due to an electrostatic field effect exerted by the bridging oxygen on that methyl group. This is an effect which has always been observed by us[20] when inverting the configuration of methyl groups H_3–C9 and H_3–C10 from the diequatorial to the diaxial disposition in this type of molecule and related oxabicyclic compounds. At this point, it was possible to conclude that **10a** and **10b** were epimers at C1′. However, because C1′ belongs to a linear side chain, with high conformational freedom, and due to the absence of hydrogen atoms on C2, it was not possible to establish by NMR studies the relative configuration at C1′. To get this stereochemical information, we submitted single crystals of isomer **10a** to X-ray diffraction analysis, which showed for **10a** the relative configuration: 1S^*, 2R^*, 4S^*, 5R^*, 1′R^* (see Fig. 2).

Aldolic cyclization of methyl ketones **10a**/**10b** using anhydrous KOH in absolute ethanol formed oxatricyclic compound **11** in 72% yield, as a unique product. It is worth noting that this aldol reaction is stereo-convergent and both epimers **10a**/**10b** give the same final product, probably via a keto–enol equilibrium at two possible levels: on precursor methylketone **10b**, which could epimerize to **10a**, and at the level of aldol intermediate **11**′, to evolve to a more stable Me–C2 versus MeO–C3 *trans*-relationship (Scheme 4). To evaluate both possibilities we carried out the aldol reaction on both epimers **10a** and **10b**, separately, stopping the reaction at 50% conversion of substrate, in order to detect possible intermediates. In the case of reaction of **10a** we exclusively observed unchanged **10a** and aldol **11**. On the other hand, in the reaction mixture coming from **10b** we observed non-reacted **10b** (8%), its epimer **10a** (42%), product **11** (49%) and intermediate **11**′ (1%). According to these findings both keto–enol equilibria are responsible for this interesting thermodynamically controlled isomerization.

The aldol cyclization reaction generated a new stereocentre at C6 and involved an existing one at C3. A simple observation of the molecular structure of **11** by Dreiding models



Scheme 4. Possible mechanism of stereo-convergence in the intramolecular aldol reaction of **10a**/**10b**.

allows one to assume that the new cyclopentanone ring should be *cis*-fused to the 8-oxabicyclo[3.2.1]octane system, due to steric constraints imposed by the tetrahydrofuran ring. Moreover, Me–C2 and MeO–C3 should be *trans*-disposed to minimize steric repulsions. Both assumptions are consistent with 3*S** and 6*S** configurations.

This stereochemical assignment was confirmed by a careful NMR study. The study required a complete assignment of ^{1}H and ^{13}C signals which was accomplished by COSY(^{1}H–^{1}H) and DEPT and/or HETCOR(^{13}C–^{1}H) NMR sequences, respectively. Hydrogens H3 and H2–C5 have important diagnostic value. Diasterotopic hydrogens H_B–C5 and H_A–C5 (see Fig. 3) appear at different field due to the deshielding electrostatic effect[21] exerted by the oxygen of HO–C6 on H_B–C5. This effect is only consistent with a *cis*-relationship between both groups. Hydrogen H_B–C5 could be easily localized because of its long-range coupling with H3 (J=1.5 Hz), which is only possible for a W-disposition[22] of both hydrogens through the carbonyl group on C4. The previous experimental observation

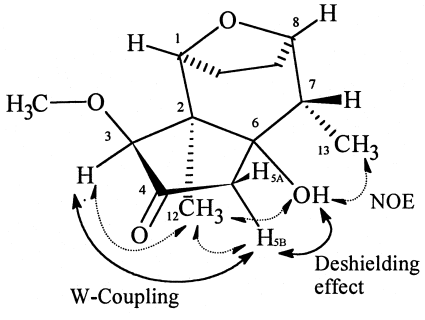


Figure 3. Illustration of couplings, deshieldings and NOE effects of stereochemical diagnostic value in **11**. Other NOE effects observed are not shown for clarity.

corroborates the *S** configuration on C3. Another way to identify the diagnostic hydrogen H_B–C5 is by observing a NOE effect[23] between this hydrogen and Me–C2 by running PS-NOESY and ROESY NMR experiments.[24] Other NOE effects with stereochemical diagnostic value, shown in Fig. 3, are: HO–C6 on both H3–C12 and H_3–C13 (which confirm an *S** configuration on C6, which is a consequence of the *cis*-joining of cyclopentanone ring) and also NOE enhancements of H_3–C12 on both H3 and H_B–C5.

At this stage, a pure sample of hydroxyketone **11** (a very stable intermediate) was analysed by chiral chromatography and ^{1}H NMR (using shift reagents and/or chiral derivatization reagents) and the ee was observed to be at the same level as in the case of precursor **4** (85%ee, see Experimental for details).

The absolute configuration of **11** was established by circular dichroism studies. The carbonyl group on C3 was considered as the chromophore (λ_{max} n→π*=297 nm) and the octant rule[25] was appropriately applied because the molecule **11** has very little conformational freedom. A positive Cotton effect was observed (see Fig. 4A) and according to the octant rule, situating the C3 carbonyl group on the reference plane, it was possible to establish for **11** the absolute configuration (1*S*, 2*R*, 3*S*, 6*S*, 7*S*, 8*R*), as shown in Fig. 4B, on the basis of bibliographic precedents.[26]

Regioselective dehydration of **11**, with generation of a non-conjugated C6–C7 double bond, was performed by using $SOCl_2$/Py at −24°C, affording compound **12** in 94% yield. Product **12** underwent two simultaneous transformations under treatment with ethanedithiol and $BF_3{\cdot}Et_2O$ at 0°C (see Scheme 3): carbonyl protection as ethanedithioketal and a concomitant regioselective oxygen-bridge cleavage to afford in 95% yield a 60:40 mixture of compounds

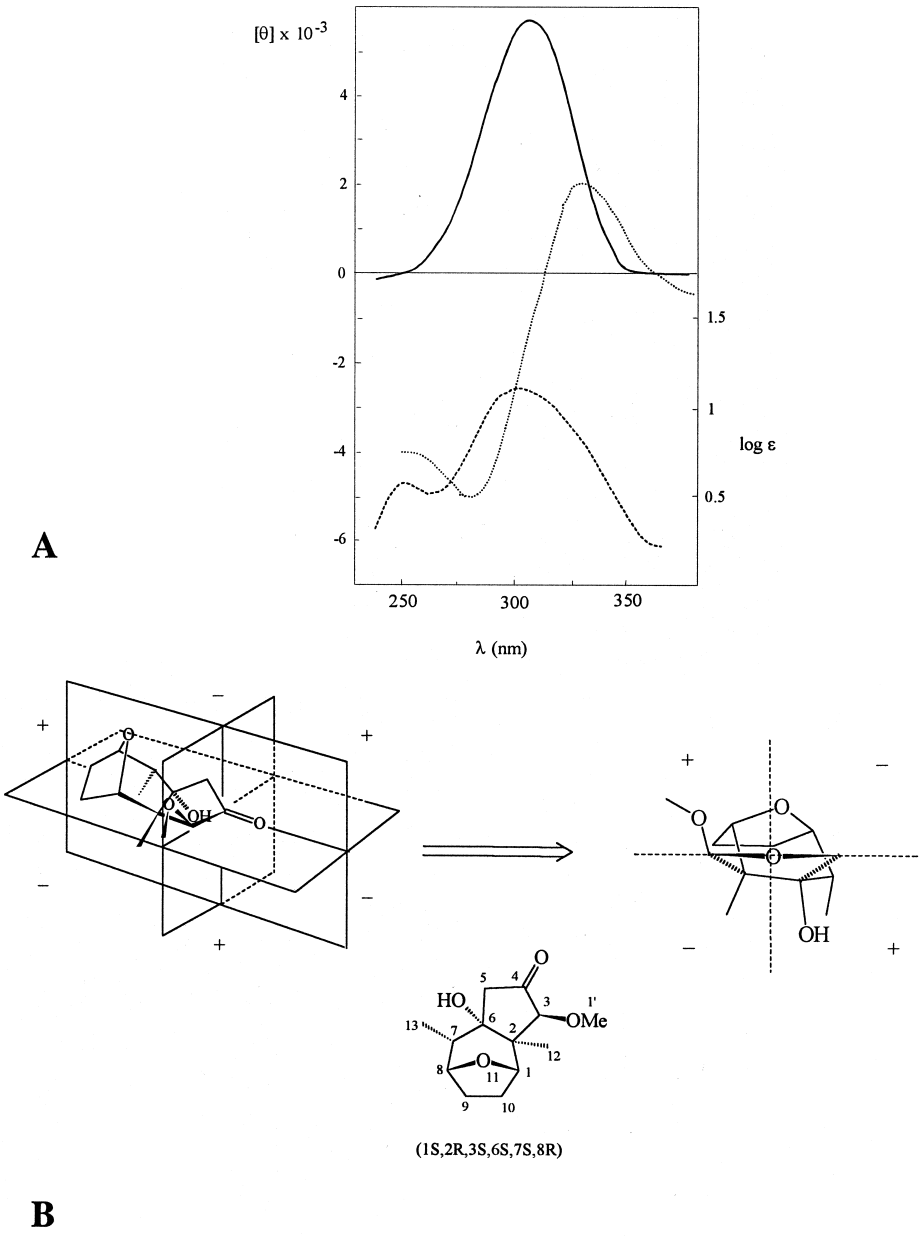


Figure 4. (A) Circular dichroism curve (—), optical rotatory dispersion curve (···) and UV curve (- - -) of **11**. [θ]: molecular optical rotation, ϵ: absorption coefficient. (B) Application of the octant rule to **11**, which shows positive Cotton effect in circular dichroism.

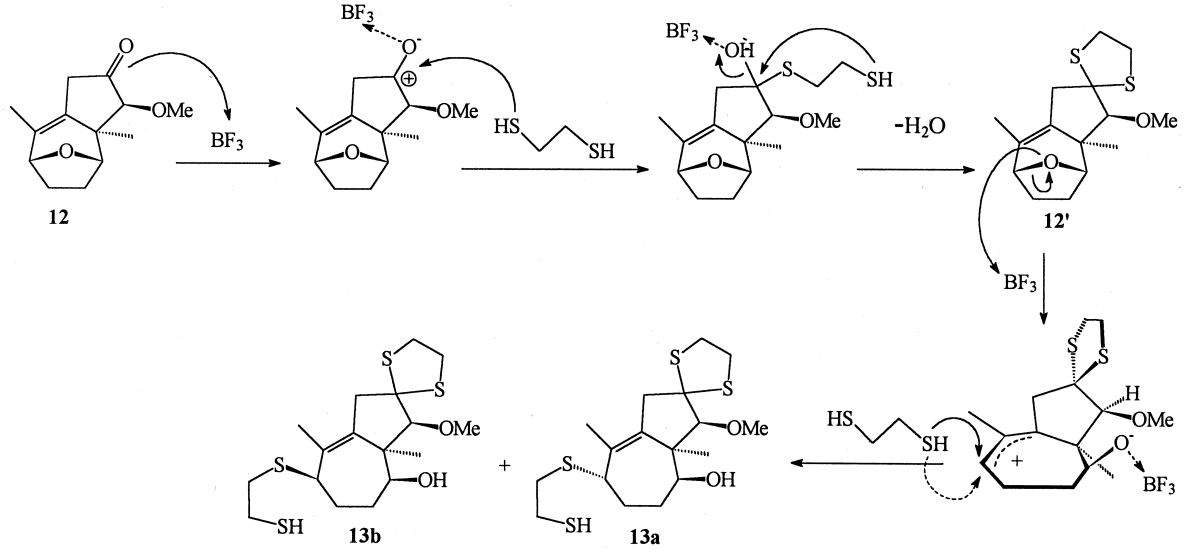
13a/**13b**, epimers at the carbon bearing the mercaptoethylenethio group.

This regioselective ring opening could be explained on the basis of an S_N1 attack of $HS–CH_2CH_2–SH$ at the allylic bridgehead induced by co-ordination of BF_3 to the bridging oxygen and formation of an allyl cation intermediate (see Scheme 5).

This mechanism was proposed after several experiments were carried out in which this reaction was performed stepwise, isolating intermediate **12′** (by using milder reaction conditions: lower proportion of Lewis acid and shorter reaction time, 20 min). This intermediate was then reacted with excess BF_3 for 6 h, obtaining **13a**/**13b** in similar ratio.

Both epimers **13a**/**13b**, resulting from the attack to both faces of the allyl carbocation (see Scheme 5), are useful for our synthetic purpose and both of them were used in the next step. They were separated by crystallization for their physical and spectroscopic characterization, but they were reacted as a mixture in the next synthetic step.

Treatment of **13a**/**13b** mixture with Raney-nickel[27] under reflux in ethanol simultaneously reduced both the dithioketal and the mercaptoethylenethio ether affording bicyclic compound **14**, as a unique stereoisomer, in 85% yield. The change of solvent, of the Raney-nickel type, and of the reaction conditions could generate a minor regioisomer of **14**, having a C7–C8 double bond, which is also useful for our synthetic purposes.



Scheme 5. Proposed mechanism of simultaneous formation of a dithioketal and the regioselective oxygen-bridge cleavage.

Hydrogenation of tetrasubstituted double bond in **14** afforded a 95:5 diastereomeric mixture of products **15a**/**15b**, respectively (separable by CC). This reaction was accomplished with high yield (90%) and good stereoselectivity (95:5, *trans*:*cis* joining, respectively) by using Pd/C(10%) as a catalyst in anhydrous MeOH at room temperature.[28] This stereoselectivity could be interpreted on the basis of two facts: (a) The disposition of the C11-methyl group sterically blocks, as an umbrella, one side of the double bond; (b) The orientation of hydroxyl and methoxy groups towards the opposite face of the double bond allows both oxygens to co-ordinate palladium atoms, which facilitates the delivery of hydrogen atoms on that face, generating a *trans*-fused bicyclo[5.3.0]decane system (see Fig. 5). More co-ordinating metal catalysts like Rh, Ru or Ir, solvents with higher dielectric constant and low reaction temperatures could increase diastereoselectivity in the hydrogenation process.[28] Research on this issue is being pursued in our laboratory.

Alcohol **15** was oxidized to ketone **16** in 95% yield by using pyridinium chlorochromate (PCC) in CH_2Cl_2.[29] Compound **16** is a versatile synthon having two functional groups that allow its further derivatization.

We can conclude that we have developed a methodology to synthesize in an enantioselective manner, functionalized *trans*-fused bicyclo[5.3.0]decanes, with induction of enantioselectivity in an early step of the synthetic pathway. We have exemplified this synthetic strategy for the preparation of a precursor of the sesquiterpenic pseudoguaiane carbon framework. Other applications of this methodology to the synthesis of biologically active natural products are under development in our laboratory.

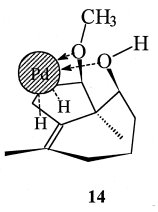


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Figure 5. Preferential co-ordinating approach of palladium atoms to the C6–C6 double bond in **14**.

Experimental

General procedures

Raw materials were obtained from commercial suppliers and used, in general, without further purification. All solvents were purified before use.[30] Purity of the chiral base (*S*,*S*′)-1,1′-dimethylbenzylamine was analysed as a hydrochloride salt by DSC techniques using a Mettler-Toledo TA8000 apparatus (purity $98.993\pm5.507\times10^{-03}$ mol%; mp=243.09°C, $[\alpha]_D^{22}=-72.4$, 3%, EtOH). *Infrared spectra* were recorded on FT-IR Nicolet 510 and Perkin–Elmer 681 spectrophotometers as thin films or as solutions, and ν_{max} was expressed in cm^{-1}. *NMR spectra* were taken in deuterared chloroform or benzene on spectrometers at 200 MHz (Gemini-200), 300 MHz (Unity-300) and/or 500 MHz (Unity-500) for ^1H NMR; at 50 MHz or 75.43 MHz for ^{13}C NMR and at 300 MHz for ^{19}F NMR spectra. All NMR spectra were expressed in δ (ppm). For ^1H NMR tetramethylsilane was used as internal standard. ^{13}C NMR spectra were referenced to the δ 77.0 ppm resonance of chloroform. For ^{19}F NMR CF_3COOH was used as internal standard. *Mass spectra* were measured on a Hewlett-Packard 5890 mass spectrometer using electron impact and/or chemical ionization techniques (conditions and the gas used are specified in each case). *Melting points* were measured on a Gallenkamp equipment. *GC analyses* were performed on a HP-8790 gas chromatograph. Standard analyses were carried out using a Hewlett-Packard-cross-linked MePhe-Silicone capillary column (l=25 m, i.d.=0.2 mm, θ=0.25 μm) using helium as a gas carrier and a FID detector (T=250°C, H_2=4.2 psi, air=2.1 psi). GC analyses were carried out under different temperature/time conditions as follows: [*Code*; initial temperature (°C); initial time (min); rate (°C/min); final temperature (°C); final

time (min)]: [A; 100; 1; 10; 290; 20]; [B; 50; 1; 5; 290; 20]; [C; 50; 1; 10; 290; 20]; [D; 40; 2; 5; 290; 20]; [E; 100; 1; 5; 290; 20]; [F; 40; 2; 5; 200; 20]; [G; 50; 1; 3; 200; 20]. For chiral GC analyses next capillary columns were used: (a) HP-Chirasil-Val, *l*=25 m, i.d.=0.25 mm; (b) FS-Lipodex E, 2,6-*O*-pentyl-3-*O*-butyric-γ-cyclodextrine; (c) Chrompack II, WCOT (wall coated open tubular) fused silica, cyclodextrine-β-2,3,6-M-19. *HPLC analyses* were conducted on an Hewlett-Packard instrument Model 1050 equipped with a Shimadzu pump, a HP-3395 integrator and an UV detector. Two types of chiral columns were used with derivatized polysaccharide stationary phases (NF102, AS25 and AS27) and/or multiple-interaction phases (Pirkle columns GR1 and TG8): (a) NF102[31] (cellulose 3,5-dimethylphenylcarbamate covalently linked to HPLC allyl-silica), 15 cm and 0.46 cm i.d.; (b) AS25 (amylose 4-chlorophenylcarbamate covalently linked to HPLC allyl-silica), 15 cm and 0.46 cm i.d.; (c) AS27 (cellulose 3,5-dichlorophenylcarbamate covalently linked to HPLC allyl-silica), 15 cm and 0.46 cm i.d.; (d) GR1 (covalently derivatized 3,5-dimethylbenzoylpropyl HPLC silica, 15 cm, 0.46 cm i.d.); (e) TG8 (covalently derivatized 3,5-dinitrobenzoylcyclohexylalanyl HPLC silica, 15 cm, 0.46 cm i.d.). Heptane and mixtures heptane/chloroform or heptane/^{i}PrOH were used as eluents in isocratic mode. In all cases a 1 mL/min flow was used. Dead times (t_0) were calculated by injecting 1,3,5-tri-*tert*-butylbenzene as a standard (non-retained in the column) and working under the same chromatographic conditions as for the analysed samples. *Elemental analyses* were obtained with a Fisons Na-1500 apparatus. *The optical rotation* was measured in a digital Perkin–Elmer 241C polarimeter, using a 10 cm long and 1 mL cell and using a sodium lamp. *The UV spectra* were recorded on a diode array UV/VIS/NIR VARIAN Model Cary-5E apparatus. *Circular dichroism and optical rotatory dispersion* studies were carried out in a spectropolarimeter Model J-730, working in the range 200–400 nm and using cells of length specified in each case. *TLC* was performed using standard commercial plates (0.25 mm) with fluorescent reagent F_{254}. The mobile phase has been indicated in each case. Products were visualized by UV or by one of the following reagents: sulfuric acid/vanillin, sulfuric acid/anisaldehyde or ninhydrine.[32] *Column chromatography* was carried out using silica gel (230–400 mesh), previously dried at 120°C for 12 h. In the case of purification of cobalt complexes, nitrogen pressure was used to run the column. *Determination of ee* Chiral GC was applied to compound **4** to determine its ee (85%), by using the chiral columns and conditions mentioned before. However, at this level the analyses are not very reproducible due to the thermal instability of silyl enol ether **4**. To obviate this problem, ee determinations were performed on the later stable intermediate **11** (this approach is possible because to transform **4** into **11** no additional chiral reagents were used, nor enantiomeric preferential crystallizations carried out). In this case, ee data were obtained from three types of analytical methods: (a) ^{1}H NMR experiments on **11** (using Eu(tfc)$_3$ as a chiral shift reagent, in 0–30% molar ratio and observing proton H12 as a set of two resolved methyl singlets); (b) ^{1}H NMR (observing H3 or H5 protons), ^{19}F NMR (observing CF_3 group) and GC analyses of enol esters (from carbonyl group on C4) derived from **11** by a quantitative, chemo- and regio-selective reaction with *R*(−) and/or *S*(+) enantiomers of Mosher acid chloride[33] (1 equiv. LDA, THF, 4 h, rt); (c) ^{1}H NMR (observing H3, H5 or H1′ protons) analyses of enol ester (from carbonyl group on C4) derived from **11** by a quantitative, chemo- and regio-selective reaction with (−)-menthyl chloroformate (1 equiv. LDA, THF, 15 h, rt). Data of ee(%) obtained from all these analyses are reproducible and within the range of 84–86%.

Preparation of 2,4-dibromo-3-pentanone, 1. Dihaloketone **1** was prepared in 75% yield according to Ref. 9. The product was purified by fractional distillation and it was percolated, prior to use, through a short column of activated neutral alumina. Three steroisomers were formed: a *meso* form and an enantiomeric pair in an 8:2 ratio. The obtained product was a colourless oil when freshly distilled.

Preparation of 2a and 2b by [4+3] cycloaddition reaction. *(a) Previous treatments: activation of copper powder.* In a 250 mL round-bottomed flask, containing commercial copper powder (10 g), a solution of iodine in acetone (2% w/v) (100 mL) was added. The suspension was stirred for 15 min and filtered through a Büchner funnel. The solid was washed with 60 mL of a 1:1 mixture of 35% (w/w) aqueous HCl and acetone, and afterwards with distilled water (100 mL) followed by acetone (50 mL). Copper powder with a metallic lustre was obtained, which was dried in high vacuum for 30 min and stored under an inert atmosphere (Ar), in darkness, in a desiccator.

(b) Activation of NaI. Sodium iodide used in cycloaddition reactions should be activated (dehydrated) before use. This activation was carried out by grinding it, followed by its dehydration in an oven at 150°C under vacuum for 24 h. It is necessary to cool it to room temperature in a desiccator prior to use.

(c) Procedure for the [4+3] cycloaddition reaction of furan with 2,4-dimethyl-2-oxyallyl cation: preparation of 2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one, 2a (and **2b***).*[9] A three-necked 1 L flask, fitted with a mechanic stirrer and a Dimroth condenser was charged, under nitrogen, with furan (50 mL, 85 mmol), freshly activated copper powder (35 g, 550 mmol), activated sodium iodide (150 g, 1 mol) and dry acetonitrile as solvent (350 mL). To the resulting suspension, 2,4-dibromo-3-pentanone (23 mL, 165 mmol) (freshly passed through a small column of activated neutral alumina), was added dropwise, at room temperature. The reaction was maintained at 55°C for 20 h (controlled by TLC and/or GC). The reaction mixture was concentrated to dryness under vacuum at 0°C. The crude oily mixture was dissolved in cold methylene chloride (100 mL), and ice water was added (100 mL) and stirring was maintained for 15 min. When copper salts precipitated, they were separated by filtration through a Büchner funnel. The organic phase (CH_2Cl_2) was decanted and kept at 0°C meanwhile the aqueous phase was extracted with cold methylene chloride (6×25 mL). All organic extracts were combined and washed with cold aqueous (25% w/w) ammonia (2×50 mL), followed by cold distilled water (2×50 mL), until no blue colour of $Cu(NH_3)_4^{2+}$ was observed. The resulting organic solution was dried over anhydrous $MgSO_4$, filtered through neutral alumina and concentrated to dryness under vacuum without heating, obtaining a thick

colourless oil (23 g, 92% yield, with respect to haloketone **1**), formed by a 80:20 diastereoisomeric mixture of cycloadducts **2a** and **2b**, respectively. The mixture was separated by flash column chromatography on silica gel (previously activated at 150°C overnight), using mixtures of hexane–ethyl acetate of increasing polarity.

2a: Thick colourless oil. IR (film) 3405, 3085 (H–Csp^2), 2971, 2876, 1713 (C=O), 1449, 1155, 1053 (C–O). ^{1}H NMR (200 MHz, $CDCl_3$) 0.96 (6H, d, J=7 Hz, H9, H10), 2.78 (2H, qd, J_1=7 Hz, J_2=4.8 Hz, H2, H4), 4.84 (2H, d, J=4.8 Hz, H1, H5), 6.34 (2H, s, H6, H7). ^{13}C NMR (50 MHz, $CDCl_3$) 10.1 (C9, C10), 50.3 (C2, C4), 82.7 (C1, C5), 133.5 (C6, C7), 208.9 (C3). MS [DIP-CI-NH_3, 70 eV, 150°C, m/z (%)] 152 (4, M), 170 (100, M+NH_4), 183 (38, M+N_2H_7). EA Calculated for $C_9H_{12}O_2$: C (71.06%), H (7.89%). Found: C (70.88%), H (7.64%). GC (Type B conditions) t_R=17.97 min. TLC (SiO_2, hexane/AcOEt 7:3) R_f=0.73 (three elutions).

2b: Thick colourless oil. IR (film) 3092 (H–Csp^2), 2975, 2938, 2878, 1711 (C=O), 1458, 1180, 1092 (C–O). ^{1}H NMR (200 MHz, $CDCl_3$) 1.36 (6H, d, J=7.5 Hz, H9, H10), 2.28 (2H, q, J=7.5 Hz, H2, H4), 4.65 (2H, s, H1, H5), 6.27 (2H, s, H6, H7). ^{13}C NMR (50 MHz, $CDCl_3$) 17.7 (C9, C10), 49.8 (C2, C4), 82.0 (C1, C5), 133.6 (C6, C7), 213.7 (C3). MS [DIP-CI-NH_3, 70 eV, 150°C, m/z (%)] 152 (2, M), 170 (100, M+NH_4), 183 (45, M+N_2H_7). EA Calculated for $C_9H_{12}O_2$: C (71.06%), H (7.89%). Found: C (70.97%), H (7.84%). GC (Type B conditions): t_R=17.28 min. TLC (SiO_2, hexane/AcOEt 7:3) R_f=0.63 (three elutions).

Hydrogenation of 2a: preparation of (2*R,4*S**)-2,4-dimethyl-8-oxabicyclo[3.2.1]octan-3-one, 3.** In a 1 L round-bottomed flask fitted with a magnetic stirring bar, an addition funnel and septa, Pd/C (10%, w/w) (3.1 g) was placed, suspended in 100 mL of absolute ethanol, under a nitrogen atmosphere (Pd catalyst is pyrophoric!). The system was purged three times with hydrogen and compound **2a** (13 g, 85.41 mmol) was added at once, dissolved in 200 mL of absolute ethanol. Once the hydrogen atmosphere was established, vigorous stirring was initiated and maintained for 2 h, at room temperature, until complete transformation of **2a** was observed by GC. The catalyst was filtered through celite, and washed with 200 mL of absolute ethanol. The organic phases were combined and concentrated to dryness under vacuum, obtaining product **3** (12.9 g, 94%) as a colourless oil. IR (film) 2973, 2880, 1713 (C=O), 1472, 1379, 1155, 1045 (C–O), 1026, 951, 930. ^{1}H NMR (200 MHz, $CDCl_3$) 0.87 (6H, d, J=7 Hz, H9, H10), 1.67 (4H, m, H6, H7), 2.72 (2H, qd, J_1=7 Hz, J_2=7 Hz, H2, H4), 4.41 (2H, m, H1, H5). ^{13}C NMR (50 MHz, $CDCl_3$) 9.6 (C9, C10), 24.8 (C6, C7), 50.3 (C2, C4), 80.9 (C1, C5), 210.2 (C3). MS [DIP-CI-NH_3, 70 eV, 150°C, m/z (%)] 154 (7, M), 172 (100, M+NH_4), 185 (52, M+N_2H_7). EA Calculated for $C_9H_{14}O_2$: C (70.13%), H (9.09%). Found: C (69.98%), H (8.95%). GC (Type C conditions) t_R=12.56 min. TLC (SiO_2, hexane/AcOEt 7:3) R_f=0.62.

Preparation of (4*S*)-2,4-dimethyl-3-trimethylsilyloxy-8-oxabicyclo[3.2.1]oct-2-ene, 4. In a 100 mL flask, previously flame-dried under vacuum, fitted with a magnetic stirring bar, (*S*,*S*′)-1,1′-dimethyldibenzylamine (2.92 g, 12.97 mmol) dissolved in anhydrous THF (10 mL) was placed, under an argon atmosphere. The solution was cooled to −78°C and 2.5 M (in hexane) butyllithium (5.178 mL, 12.97 mmol) was added by syringe. After addition the reaction mixture was allowed to reach rt (30 min) and then cooled again to −78°C. At this temperature, lithium chloride (137 mg, 3.24 mmol) dissolved in anhydrous THF (5 mL) and ketone **3** (1 g, 6.48 mmol) dissolved in anhydrous THF (10 mL) were added successively and in this order. After 4 h, highly pure (>99%) trimethylsilylchloride (2.86 mL, 22.69 mmol) was added dropwise. The mixture was stirred for 30 min at −78°C and then at rt for 1 h. Solvent was removed by vacuum, 50 mL of anhydrous pentane were added and the dissolution filtered out by cannula, in order to remove most of the LiCl. The organic phase was washed with cold distilled water (5 mL) and extracted with cold (0°C) 0.1 M HCl (3×10 mL), to separate the chiral base, and then with cold distilled water again; it was dried over anhydrous $MgSO_4$, filtered and concentrated to dryness under vacuum (without heating). Silyl enol ether **4** was obtained as a colourless oil (1.46 g, 99% yield). The chiral amine present as a hydrochloride salt in the acidic aqueous phase was recovered by adding 1 M aq. NaOH up to pH=8 and extracting with diethyl ether (5×10). The organic phase was washed with water, dried over $MgSO_4$, filtered and concentrated to dryness, obtaining 2.8 g (95% recovery) of a thick colourless oil. This amine should be tested for purity prior to use and recrystallized as a hydrochloride salt if necessary. IR (film) 2959, 2869, 1680 (C=C), 1460, 1252, 1202, 1122, 1049 (C–O), 893, 843 (Si–C). ^{1}H NMR (300 MHz, $CDCl_3$) 0.18 (9H, s, $SiMe_3$), 0.91 (3H, d, J=7.2 Hz, H10), 1.52 (3H, d, J=2.2 Hz, H9), 1.83 (4H, m, H6, H7), 2.82 (1H, m, H4), 4.25 (1H, dd, J_1=2.4 Hz, J_2=2.7 Hz H1), 4.35 (1H, ddd, J_1=4.0 Hz, J_2=5.5 Hz, J_3=1.3 Hz, H5). ^{13}C NMR (50 MHz, $CDCl_3$) 0.0 ($SiMe_3$), 11.6 (C10), 12.3 (C9), 22.6 (C7), 32.5 (C6), 39.0 (C4), 76.9 (C5), 78.9 (C1), 126.3 (C2), 127.9 (C3). MS [DIP-CI-NH_3, 70 eV, 150°C, m/z (%)]: 226 (100, M), 227 (24, M+H), 244 (25, M+NH_4). EA Calculated for $C_{12}H_{22}O_2Si$: C (63.68%), H (9.80%). Found: C (63.71%), H (9.78%). GC (Type C conditions) t_R= 15.51 min. TLC (SiO_2; hexane/ether, 9:1) R_f=0.28.

Preparation of 3,3-dimethoxypropyne, 6 from 1,2-dibromo-3,3-dimethoxypropane, 5. In a three-neck round-bottomed 250 mL flask, fitted with a mechanical stirrer, an addition funnel, and a Dimroth condenser, tetrabutylammonium hydrogensulfate (25 g, 73.6 mmol) and water (25 mL) were placed. The mixture was vigorously stirred to get a thick homogeneous paste. From the addition funnel, 1,2-dibromo-3,3-dimethoxypropane **5** (7.25 g, 27.7 mmol) dissolved in pentane (30 mL) was slowly added at 10°C. Intermediate **5** was prepared according to Refs. 9,16. The addition funnel was then charged with a cold solution of NaOH (15 g, 0.375 mol) in 25 mL of distilled water. This alkaline dissolution was slowly added during a period of 10 min, and the resulting mixture was vigorously stirred for 2 h at 10°C. The reaction mixture was cooled down to 0°C and neutralized with 25% (v/v) sulfuric acid. The formed sodium sulfate was filtered out by cannula, washing it with pentane (3×10 mL). The liquid filtrate was transferred to an addition funnel and the aqueous phase

decanted and extracted with pentane (4×5 mL). All organic phases were combined, dried over anhydrous $MgSO_4$, filtered and submitted to a careful fractional distillation (in a 30 cm Vigreux column), at atmospheric pressure, obtaining 1.7 g (60%) of acetal **6** as a colourless volatile oil. IR (film) 3276, 2940, 2834, 2128 (C≡C), 1358, 1113, 1061 (C–O), 966. ^{1}H NMR (200 MHz, $CDCl_3$) 2.51 (1H, d, J=1.8 Hz, H3), 3.32 (9H, s, H1′), 5.09 (1H, d, J=1.8 Hz, H1). ^{13}C NMR (50 MHz, $CDCl_3$) 52.4 (C1′), 74.1 (C3), 78.1 (C2), 92.6 (C1). MS [DIP-CI-NH_3, 70 eV, 150°C, *m*/*z* (%)] 69 (100, M−OMe), 118 (3, M+NH_4), 135 (4, M+N_2H_7). EA Calculated for $C_5H_8O_2$: C (59.97%), H (8.06%). Found: C (60.01%), H (8.10%). GC (Type D conditions) t_R=4.41 min. TLC (SiO_2, hexane/ether 9:1) R_f=0.36.

Synthesis of hexacarbonyl μ-{η^4-[3,3-dimethoxypropyne]}-dicobalt(Co–Co), 7. In a 100 mL flask, previously flame-dried under vacuum and purged with argon, was placed dicobaltoctacarbonyl (3.281 g, 9.6 mmol) dissolved in 50 mL of anhydrous pentane. The system was cooled to 0°C and 3,3-dimethoxypropyne **5** (800 mg, 8 mmol) was added by cannula. The cooling bath was removed and the mixture stirred at room temperature for 2 h. CO gas released in the reaction was evacuated via a bubblier to a well-ventilated lab hood. The reaction mixture was filtered through a short column packed with neutral alumina (previously activated at 140°C for 2 h), to remove polymeric materials and inorganic compounds, obtaining product **7** (3 g, 100% yield) as a dark red oil. IR (film) 2934, 2834 (H–Csp^3), 2099 (C≡C), 2056, 2024 (C=O), 1321, 1103, 1078 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) 3.47 (6H, s, H1′), 5.38 (1H, s, H3), 6.04 (1H, s, H1). ^{13}C NMR (75.43 MHz, $CDCl_3$) 54.3 (C1′), 71.0 (C3), 103.9 (C1), 199.4, 201.5 ($Co_2(CO)_6$). MS [DIP-EI, 70 eV, 150°C, *m*/*z* (%)]: 358 (2, M−CO), 330 (2, M−2CO), 302 (3, M−3CO), 274 (3, M−4CO), 246 (3, M−5CO), 218 (4, M−6CO), 159 (10, M−6CO−Co), 100 (7, M−6CO−2Co). EA Calculated for $C_{11}H_8O_8Co_2$: C (34.22%), H (2.09%). Found C (34.30%), H (1.98%). TLC (SiO_2, hexane/ether 9:1) R_f=0.37.

Nicholas reaction: preparation of hexacarbonyl μ-{η^4-[2,4-dimethyl-2-(1-methoxy-2-propyn-1-yl)-8-oxabicyclo-[3.2.1]octan-3-one]}dicobalt(Co–Co), 8a/8b.

In an oven-dried 10 mL flask, fitted with septa and a magnetic stirring bar, cobalt complex **7** (120 mg, 0.311 mmol) dissolved in 1 mL of dry methylene chloride was placed under argon atmosphere. The solution was cooled to 0°C and $BF_3{\cdot}OEt_2$ (96 μL, 0.777 mmol) was added via syringe. After 30 min, silyl enol ether **4** (58 mg, 0.259 mmol) dissolved in 2 mL of CH_2Cl_2 was added via cannula. The system was stirred under these conditions for 5 min, the cooling bath was removed and the mixture was stirred for 1.5 h at room temperature (control by TLC). The reaction mixture was cooled to 0°C, quenched with triethylamine (72 μL, 0.518 mmol) and percolated through a short column of activated neutral alumina. Finally it was concentrated to dryness under vacuum (without heating), obtaining a dark red oil of a 1:1 mixture of complexes **8a**/**8b** (99 mg, 75% yield). This product was reacted as a mixture, but in order to physically and spectroscopically characterize both diastereoisomers an aliquot of the crude mixture was submitted to flash column chromatography on activated neutral alumina eluting with mixtures of dry pentane and dry ether of increasing polarity. Dry nitrogen was used to run the column.

8a: Dark red thick oil. IR (film) 2965, 2095, 2053, 2024 $(CO)_6$, 1717 (C=O), 1653, 1554, 1506, 1472, 1379, 1277, 1178, 1092,1045 (C–O). ^{1}H NMR (200 MHz, $CDCl_3$) 0.95 (3H, d, J=7.6 Hz, H10), 0.98 (3H, s, H9), 1.80–1.50 (4H, m, H6, H7), 2.84 (1H, dq, J_1=6.0 Hz, J_2=7.6 Hz, H4), 3.74 (3H, s, OMe), 4.52 (1H, d, J=7.3 Hz, H1), 4.54 (1H, dd, J_1=2.6 Hz, J_2=6.0 Hz, H5), 5.24 (1H, s, H3′), 5.74 (1H, s, H1′). ^{13}C NMR (75.43 MHz, $CDCl_3$) 9.8 (C10), 11.7 (C9), 24.7, 24.9 (C6, C7), 48.8 (C4), 60.6 (C1″), 72.5 (C3′), 81.6, 81.8 (C1, C5), 83.1 (C1′), 199.5 $(CO)_6$, 209.4 (C3). MS [DIP-EI, 70 eV, 150°C, *m*/*z* (%)] 480 (1, M−CO), 452 (6, M−2CO), 424 (4, M−3CO), 396 (6, M−4CO), 368 (5, M−5CO), 340 (12, M−6CO), 281 (2, M−6CO−Co), 222 (4, M−6CO−2Co), 105 (100). EA Calculated for $C_{19}H_{18}O_9Co_2$: C (44.90%), H (3.57%). Found C (45.01%), H (3.62%). TLC (SiO_2, hexane/AcOEt 9:1, two elutions) R_f=0.53.

8b: Dark red thick oil. IR (film) 2964, 2095, 2052, 2024 $(CO)_6$, 1717 (C=O), 1653, 1554, 1506, 1472, 1379, 1277, 1178, 1092, 1045 (C–O). ^{1}H NMR (200 MHz, $CDCl_3$) 0.993 (3H, d, J=6.7 Hz, H10), 0.996 (3H, s, H9), 1.80–150 (4H, m, H6, H7), 3.12 (1H, dq, J_1=6.6 Hz, J_2=6.7 Hz, H4), 3.48 (3H, s, OMe), 4.49 (1H, d, J=7.2 Hz, H1), 4.51 (1H, dd, J_1=4.9 Hz, J_2=6.6 Hz, H5), 5.33 (1H, s, H3′), 6.10 (1H, s, H1′). ^{13}C NMR (75.43 MHz, $CDCl_3$) 9.9 (C10), 12.5 (C9), 24.4, 24.9 (C6, C7), 47.5 (C4), 59.8 (OMe), 72.8 (C3′), 81.5, 81.6 (C1, C5), 84.9 (C1′), 199.5 $(CO)_6$, 209.2 (C3). MS [DIP-EI, 70 eV, 150°C, *m*/*z* (%)] 480 (1, M−CO), 452 (5, M−2CO), 424 (4, M−3CO), 396 (6, M−4CO), 368 (5, M−5CO), 340 (13, M−6CO), 281 (2, M−6CO−Co), 222 (4, M−6CO−2Co), 105 (100). EA Calculated for $C_{19}H_{18}O_9Co_2$: C (44.90%), H (3.57%). Found C (44.88%), H (3.55%). TLC (SiO_2, hexane/AcOEt 9:1, two elutions) R_f=0.44.

Preparation of 2,4-dimethyl-2(1-methoxy-2propyn-1-yl)-8-oxabicyclo[3.2.1]octan-3-one, 9a/9b. In a 10 mL flask fitted with a magnetic stirring bar, a 1:1 mixture of complexes **8a**/**8b** (80 mg, 0.157 mmol), dissolved in 5 mL of dry acetone, was placed. Triethylamine (44 μL, 0.315 mmol) was added and the mixture cooled to 0°C. Next, cerium ammonium nitrate (431 mg, 0.787 mmol) was added and the mixture stirred at 0°C for 1 h (control by TLC until cobalt complex was completely oxidized). Solvent was removed under vacuum and the residue was treated with a mixture of ice-water/triethylamine (25 mL/0.1 mL) and extracted with diethyl ether (6×5 mL) (if emulsions are formed they could be resolved by ultrasound in a cleaning bath or by centrifugation). All ethereal extracts were combined, washed with a saturated aqueous solution of sodium hydrogencarbonate (5 mL) and with brine, then dried over anhydrous sodium sulfate, filtered and finally percolated trough a short column packed with celite/neutral alumina 1:1. Solvent was removed under vacuum, without heating, obtaining a 1:1 mixture of diastereoisomeric acetylenic compounds **9a**/**9b** (33 mg, 94% yield) as a white solid.

9a: White solid. Mp 128°C (diethyl ether). IR (film) 3268, 2940, 2100 (C≡C), 1715 (C=O), 1092, 1049, 1026 (C–O). ^{1}H NMR (200 MHz, $CDCl_3$) 0.94 (3H, d, J=6.6 Hz, H10), 1.05 (3H, s, H9), 1.80–1.45 (4H, m, H6, H7), 2.42 (1H, d, J=2.2 Hz, H3′), 2.83 (1H, dq, J_1=6.2 Hz, J_2=6.6 Hz, H4), 3.49 (3H, s, OMe), 4.47 (1H, dd, J_1=6.2 Hz, J_2=4.9 Hz, H5), 4.54 (1H, d, J=7.2 Hz, H1), 4.78 (1H, d, J=2.2 Hz, H1′). ^{13}C NMR (50 MHz, $CDCl_3$) 9.9 (C10), 11.8 (C9), 24.7 (C7), 25.0 (C6), 48.6 (C4), 57.6(OMe), 60.4 (C2), 72.8 (C3′), 76.4 (C1′), 80.0 (C1), 81.3 (C5), 28.2 (C3). MS [DIP-CI-NH_3, 70 eV, 150°C, m/z (%)]: 222 (1, M), 223 (15, M+H), 240 (100, M+NH_4), 257 (11, M+N_2H_7). EA Calculated for $C_{13}H_{18}O_3$: C (70.24%), H (8.16%). Found: C (69.93%), H (8.02%). $[\alpha]_D^{22}$=5.0° (0.4%, EtOH). GC (Type C conditions) t_R=16.78 min. TLC (SiO_2, hexane/AcOEt 9:1, two elutions) R_f=0.42.

9b: Thick colourless oil. IR (film) 3255, 2934, 2102 (C≡C), 1715 (C=O), 1451, 1379, 1095 (C–O), 1047, 1028. RMN ^{1}H (200 MHz, $CDCl_3$) 0.95 (3H, d, J=6.7 Hz, H10), 1.08 (3H, s, H9), 1.8–1.4 (4H,m, H6, H7), 2.56 (1H, d, J=2.2 Hz, H3′), 2.92 (1H, dq, J_1=4.9 Hz, J_2=6.7 Hz, H4), 3.36 (3H, s, OMe), 4.40–4.60 (2H, m, H1, H5), 4.89 (1H, d, J=2.2 Hz, H1′). RMN ^{13}C (50 MHz, $CDCl_3$) 8.9 (C10), 11.1 (C9), 23.3 (C7), 23.8 (C6), 46.2 (C4), 56.3 (OMe), 58.2 (C2), 74.2 (C3′), 75.7 (C1′), 80.5 (C1), 80.6 (C5), 208.2 (C3). MS [DIP-CI-NH_3, 70 eV, 150°C, m/z (%)] 222 (1, M), 223 (14, M+H), 240 (100, M+NH_4), 257 (10, M+N_2H_7). EA Calculated for $C_{13}H_{18}O_3$: C (70.27%), H (8.10%). Found: C (70.01%), H (8.12%). $[\alpha]_D^{22}$=−8.0° (0.4%, EtOH). GC (Type C conditions) t_R=17.32 min. TLC (SiO_2, hexane/AcOEt 9:1, two elutions) R_f=0.32.

Synthesis of 2,4-dimethyl-2-(1-methoxy-2-oxopropyl)-8-oxabicyclo-[3.2.1]octan-3-ona, 10a/10b. *(a) Preparation of Hg(II) p-toluenesulfonamidate.* *p*-Toluenesulfonamide (6.7 g, 39.12 mmol) and Hg(II) oxide (4.24 g, 19.55 mmol) were finely ground until an homogeneous solid mixture was obtained. This mixture was placed in a porcelain crucible and heated in an oven at 200°C under vacuum for 3 h until orange colour disappeared. The solid was cooled down and ground again and it was transferred to a 100 mL flask. Absolute ethanol was added (50 mL) and the system was maintained under reflux for 30 min and filtered when hot. The solid was dried under vacuum obtaining Hg(II) *p*-toluenesulfamidate (7.3 g, 70% yield) as a white solid. IR (KBr) 3305 (N–H), 3039 (Csp^2–H), 2917, 1912, 1653, 1601 (C=C), 1400, 1265, 1229, 1134 (S=O), 1088, 1018.

*(b) Hydration of **9a**/**9b**: preparation of methyl ketones **10a**/**10b**.* To a solution of **9a**/**9b** (1:1) (1.18 g, 4.23 mmol) in 150 mL of EtOH/water (85:15), Hg(II) *p*-toluenesulfonamidate (3.73 g, 6.90 mmol) was added and the resulting suspension was refluxed, under vigorous stirring, for 24 h (monitoring by TLC and/or GC). The resultant yellowish solution was allowed to reach room temperature and excess $(NH_4)_2S$ (6.5 mL, 9.6 mmol) was added to precipitate Hg(II) salts as black HgS. The black suspension was filtered through a pad of sand–Celite–silica gel using a fritted funnel. The solvent was removed by rotatory evaporation and 200 mL of ether and 30 mL of brine were added. After shaking vigorously, the aqueous solution was discarded and the ethereal solution extracted with 2 M aqueous NaOH (3×10 mL) (to remove $TsNH_2$) then washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to dryness, obtaining 1.04 g (82% yield) of a crystalline white solid. The product was formed by a 1:1 mixture of diastereoisomers **10a** and **10b**, which was used as a mixture for next synthetic step. However, it was possible to separate both stereoisomers by flash column chromatography on silica gel, eluting with hexane/ether mixtures of increasing polarity.

10a: White solid. Mp 121°C (diethyl ether). IR (film) 2963, 1717 (C=O), 1468, 1379, 1354, 1219, 1103, 1047, 1030 (C–O). ^{1}H NMR (500 MHz, $CDCl_3$) 0.86 (3H, s, H9), 0.93 (3H, d, J=6.7 Hz, H10), 1.75 (2H, m, $W_{1/2}$=30 Hz, H6 and H7), 1.6–1.9 (2H, m, H6, H7), 2.16 (3H, s, H3′), 3.21 (1H, dq, J_1=4.9 Hz, J_2=6.7 Hz, H4), 3.58 (3H, s, OMe), 4.44 (1H, s, H1′), 4.47 (1H, d, J=5.5 Hz, H1), 4.48 (1H, dd, J_1=4.9 Hz, J_2=6.2 Hz, H5). ^{13}C NMR (75.43 MHz, $CDCl_3$) 9.8 (C10), 11.5 (C9), 24.5, 24.8 (C6, C7), 27.5 (C3′), 48.0 (C4), 59.9 (C2), 60.2 (OMe), 80.5, 82.3 (C1, C5), 88.3 (C1′), 208.2 (C3), 212.8 (C2′). MS [DIP-CI-NH_3, 70 eV, 150°C, m/z (%)]: 240 (1, M), 241 (4, M+H), 258 (100, M+NH_4), 275 (10, M+N_2H_7). EA Calculated for $C_{13}H_{20}O_4$: C (65.00%), H (8.33%). Found: C (65.20%), H (8.30%). $[\alpha]_D^{22}$=−1.3° (0.4%, EtOH). GC (Type C conditions) t_R=19.08 min. TLC (SiO_2, hexane/ether 1:1) R_f=0.31.

10b: Thick colourless oil that crystallizes below 0°C. IR (film) 2924, 2850, 1713 (C=O), 1450, 1375, 1099, 1040, 1030 (C–O). ^{1}H NMR (500 MHz, $CDCl_3$) 0.92 (3H, s, H9), 0.97 (3H, d, J=6.7 Hz, H10), 1.5–1.9 (2H, m, H6, H7), 2.24 (3H, s, H3′), 2.92 (1H, qd, J_1=6.7 Hz, J_2=5.1 Hz, H4), 3.34 (3H, s, OMe), 4.43 (1H, d, J=6.5 Hz, H1), 4.43 (1H, s, H1′), 4.49 (1H, dd, J_1=6.5 Hz, J_2=5.3 Hz, H5). ^{13}C NMR (75.43 MHz, $CDCl_3$) 9.9 (C10), 12.8 (C9), 24.5, 24.6 (C6, C7), 27.8 (C3′), 47.6 (C4), 58.4 (C2), 59.6 (OMe), 80.0, 81.3 (C1, C5), 88.4 (C1′), 208.2 (C3), 211.6 (C2′). MS [DIP-CI-NH_3, 70 eV, 150°C, m/z (%)] 240 (1, M), 241 (4, M+H), 258 (100, M+NH_4), 275 (9, M+N_2H_7). EA Calculated for $C_{13}H_{20}O_4$: C (65.00%), H (8.33%). Found: C (65.15%), H (8.25%). $[\alpha]_D^{22}$=−1.8° (0.6%, EtOH). GC (Type C conditions): t_R=19.40 min. TLC (SiO_2, hexane/ether 1:1) R_f=0.24.

(1*S*,2*R*,3*S*,6*S*,7*S*,8*R*)-2,7-Dimethyl-6-hydroxy-3-methoxy-11-oxatricyclo[6.2.1.0^{2,6}]undecan-4-one, 11. In an oven-dried 250 mL flask fitted with a magnetic stirring bar and in nitrogen atmosphere, **10a**/**10b** (1:1) (890 mg, 3.712 mmol) dissolved in 30 mL of absolute ethanol was placed. Anhydrous KOH (2.29 g, 40.837 mmol) dissolved in 100 mL of absolute ethanol was added, and the mixture was stirred at room temperature for 10 h. Solvent was removed by rotatory evaporator, distilled water was added (100 mL) and the solution was treated with 2 M HCl, at 0°C, to reach pH=6–7. The resultant aqueous solution was extracted with ether (10×25 mL) and all organic phases were combined, dried over $MgSO_4$, filtered and concentrated to dryness, obtaining product **11** (623 mg, 72%) as a white crystalline solid. This product was purified by flash column chromatography on silica gel, using mixtures of hexane/ether of increasing polarity as a mobile phase. Mp 149°C (diethyl ether). IR (film) 3395 (O–H), 2971, 1748 (C=O), 1468, 1258, 1150, 1105 (C–O), 987, 957, 916.

^{1}H-NMR (500 MHz, $CDCl_3$) 0.98 (3H, s, H12), 0.93 (3H, d, J=7.0 Hz, H13), 1.55 (1H, br s, OH), 1.79 (1H, dd, J_1=8.0 Hz, J_2=7.5 Hz, $H9_B$), 1.87 (1H, dd, J_1=8.0 Hz, J_2=8.5 Hz, $H10_B$), 1.94 (1H, qd, J_1=7.0 Hz, J_2=4.0 Hz, H7), 2.03 (1H, d, J=19.5 Hz, $H5_A$), 2.1–2.2 (2H, m, $H9_A$, $H10_A$), 2.49 (1H, dd, J_1=19.5 Hz, J_2=1.5 Hz, $H5_B$), 3.63 (3H, s, OMe), 4.03 (1H, d, J=8.0 Hz, H1), 4.13 (1H, dd, J_1=7.5 Hz, J_2=4.0 Hz, H8), 4.37 (1H, d, J=1.5 Hz, H3). ^{13}C NMR (75.43 MHz, $CDCl_3$) 9.9 (C12), 12.3 (C13), 23.9 (C9), 24.7 (C10), 41.3 (C7), 48.9 (C5), 49.6 (C2), 60.6 (OMe), 72.9 (C6), 77.3 (C1), 79.0 (C8), 87.2 (C3), 213.2 (C4). COSY ^{1}H–^{1}H (500 MHz, $CDCl_3$) couplings: H7–H13, H8–$H9_B$, H1–$H10_B$, H3–$H5_B$ (*W*-coupling), $H9_A$–$H9_B$, $H10_A$–$H10_B$, $H9_A$–$H10_A$, $H9_A$–$H10_B$, $H9_B$–$H10_A$, $H9_B$–$H10_B$, $H5_A$–$H5_B$. NOESY (500 MHz, $CDCl_3$): H1–H12, H8–H13, H12–OH, H13–OH, $H5_B$–H13, H3–$H5_B$, H3–H1′, $H9_B$–H13, $H10_B$–H12, H3–H12. MS [DIP-CI-NH_3, 70 eV, 150°C, *m*/*z* (%)] 240 (2, M), 241 (1, M+H), 258 (100, M+NH_4), 275 (32, M+N_2H_7). EA Calculated for $C_{13}H_{20}O_4$: C (65.00%), H (8.33%). Found: C (65.30%), H (8.30%). $[\alpha]_D^{23}$=+20° (1%, $CHCl_3$). UV [λ_{max}, nm, (ϵ)] 297 (14), 257 (7), 246 (8). CD [λ, nm, ($\Delta\epsilon$), l=0.02 cm, c=6.25×10^{-2} M, $CHCl_3$]: 308 (1.229), 220 (−0.708). ROD (λ_{max}, nm, [α], l=0.02 cm, c=6.25×10^{-2} M, $CHCl_3$): 329 (1.33×10^3), 282 (−3.38×10^3). GC (Type C conditions) t_R=20.68 min. CCF (SiO_2, hexane/ether 1:1, 2 elutions) R_f=0.15.

Synthesis of (1*S*,2*R*,3*S*,8*R*)-3-methoxy-2,7-dimethyl-11-oxatricyclo[6.2.1.0^{2,6}]undec-6-en-4-one, 12. In a 25 mL flask fitted with a septum, an argon atmosphere and a magnetic stirring bar, substrate **11** (150 mg, 0.62 mmol), dissolved in dry pyridine (10 mL) was placed. The system was cooled to −24°C and freshly distilled (from quinoline) thionyl chloride (91 μL, 1.25 mmol) was added by syringe. The mixture was stirred at −24°C for 2 h (control by TLC and/or GC). Aqueous 1 M HCl (100 mL) was added and the aqueous phase extracted with ether (4×25 mL). All organic phases were combined, dried over $MgSO_4$, filtered and concentrated by rotatory evaporation, obtaining product **12** (130 mg, 94% yield) as a colourless oil. IR (film) 2961, 2830, 1757 (C=O), 1445, 1211, 1101, 1076, 1011 (C–O), 962. ^{1}H NMR (300 MHz, $CDCl_3$) 0.93 (3H, s, H12), 1.70 (3H, d, J=1.8 Hz, H13), 1.8–2.2 (4H, m, H9, H10), 2.75 (1H, dd, J_1=20.5 Hz, J_2=1.8 Hz, H5), 2.88 (1H, d, J=20.5 Hz, H5), 3.64 (3H, s, OMe), 3.87 (1H, s, H3), 4.25 (1H, d, J=6.6 Hz, H1), 4.36 (1H, d, J=6.2 Hz, H8). ^{13}C NMR (75.43 MHz, $CDCl_3$) 15.4 (C12), 16.6 (C13), 25.5, 30.7 (C9, C10), 37.2 (C5), 48.4 (C2), 60.1 (OMe), 76.7 (C1), 77.1 (C8), 88.7 (C3), 125.2 and 137.6 (C6 and C7), 213.5 (C4). MS [DIP-CI-NH_3, 70 eV, 150°C, *m*/*z* (%)]: 222 (1, M), 223 (2, M+H), 240 (100, M+NH_4), 257 (14, M+N_2H_7). EA Calculated for $C_{13}H_{18}O_3$: C (70.23%), H (8.17%). Found: C (69.84%), H (7.99%). $[\alpha]_D^{22}$=+171.7° (1.6%, $CHCl_3$). GC (Type C conditions) t_R=18.84 min.

Preparation of 1,6-dimethyl-9,9-(1,2-ethylendithio)-10-methoxy-5-(2-mercaptoethylenthio)-bicyclo[5.3.0]-dec-6-en-1-ol, 13a/13b. Compound **12** (30 mg, 0.135 mmol) dissolved in anhydrous benzene (2 mL) was placed in an oven-dried 10 mL flask fitted with a septum and a magnetic stirring bar. The system was purged with argon and 1,2-ethanedithiol (0.75 mL, 9.92 mmol) was added by syringe. The mixture was cooled to 0°C and BF_3·OEt_2 (38 μL, 0.311 mmol) was added at once by syringe. Stirring was maintained under these conditions for 6 h (monitoring by TLC and/or GC). The reaction mixture was dissolved in ether (50 mL) and washed with saturated aqueous solution of sodium hydrogencarbonate (2×5 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated to dryness under high vacuum for 5 h (to remove excess ethanedithiol), obtaining product **13** (50 mg, 95% yield) as a thick stinking oil. Product **13** was a 60:40 mixture of diastereoisomers **13a**/**13b**, epimers on C5. Both isomers were useful from the synthetic point of view (because stereocentre on C5 disappeared in next synthetic step) and they were reacted as a mixture. However, both isomers were separated for their characterization by flash column chromatography on silica gel, using pentane/ether mixtures of increasing polarity as eluents.

13a: Malodorous white solid, Mp=126–127°C (ether). IR (film) 3488 (O–H), 2923, 2546 (S–H), 1699 (C=C), 1439, 1420, 1204, 1117 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) 1.31 (3H, s, H11), 1.75 (3H, d, J=1.5 Hz, H12), 1.50–1.80 (2H, m, H3), 2.13–2.51 (2H, m, H4), 2.70–2.75 (4H, m, H1′, H2′), 2.88 (1H, d, J=18.6 Hz, H8), 3.12 (1H, d, J=18.6 Hz, H8), 3.2–3.4 (4H, m, H1″ H2″), 3.42 (1H, dd, J_1=8.4 Hz, J_2=3.5 Hz, H5), 3.71 (3H, s, OMe), 3.66–3.73 (1H, m, H2), 4.54 (1H, s, H10). ^{13}C NMR (75.43 MHz, $CDCl_3$) 20.2 (C12), 22.7 (C11), 23.9 (C3), 24.8 (C4), 25.7 (C2′), 37.1 (C1′), 38.3, 41.1 (C1″, C2″), 51.2 (C8), 52.1 (C5), 54.7 (C1), 61.7 (OMe), 70.1 (C9), 70.5 (C2), 89.3 (C10), 129.9, 137.2 (C7, C6). MS [DIP-CI-NH_3, 70 eV, 150°C, *m*/*z* (%)]: 299 (10, M−$C_2H_4S_2$), 316 (20, M−$C_2H_4S_2$+NH_4), 393 (56, M−H), 394 (21, M), 395 (20, M+H), 410 (100, M+16), 411 (35, M+NH_3), 412 (18, M+NH_4). EA Calculated for $C_{17}H_{22}O_2S_4$: C (52.84%), H(5.74%), and S (33.13%). Found: C (52.86%), H (5.81%), and S (33.02%). $[\alpha]_D^{22}$=36.78° (1.15%, $CHCl_3$). TLC (SiO_2, hexane/ether 4:6) R_f=0.37.

13b: Stinking colourless thick oil, IR (film) 3444 (O–H), 2925, 2546 (S–H), 1699 (C=C), 1420, 1375, 1273, 1204, 1119 (C–O). ^{1}H NMR (300 MHz, $CDCl_3$) 1.24 (3H, s, H11), 1.72 (3H,s, H12), 1.80–2.40 (4H, m, H4, H3), 2.70-2.80 (4H, m, H1′, H2′), 3.02 (1H, d, J=18.3 Hz, H8), 3.11(1H, d, J=18.3 Hz, H8), 3.20–3.30 (4H, m, H1″, H2″), 3.30–3.42 (1H, m, H5), 3.69 (3H, s, OMe), 3.60–3.80 (1H, m, H2), 4.37 (1H, s, H10). ^{13}C NMR (75.43 MHz, $CDCl_3$) 16.8 (C12), 20.3 (C11), 24.3 (C3), 28.2 (C4), 29.5 (C2′), 35.5 (C1′), 38.5, 41.2 (C1″, C2″), 50.4 (C5), 51.4 (C8), 54.5 (C1), 61.7 (OMe), 69.5 (C9), 72.1 (C2), 89.3 (C10), 128.6, 136.6 (C7, C6). MS [DIP-CI-NH_3, 70 eV, 150°C, *m*/*z* (%)]: 299 (13, M−$C_2H_4S_2$), 316 (16, M−$C_2H_4S_2$+NH_4), 393 (44, M−H), 394 (10, M), 395 (9, M+H), 410 (100, M+16), 411 (22, M+NH_3), 412 (20, M+NH_4). EA Calculated for $C_{17}H_{22}O_2S_4$: C (52.84%), H(5.74%), and S (33.13%). Found: C (52.79%), H (5.69%), and S (33.21%). $[\alpha]_D^{22}$=−14.61° (1%, EtOH). TLC (SiO_2, hexane/ether 4:6) R_f=0.44.

Synthesis of (1*R*,2*S*,10*R*)-1,6-dimethyl-10-methoxy-bicyclo[5.3.0]dec-6-en-2-ol, 14. A 25 mL round-bottomed flask, fitted with a magnetic stirring bar and a rubber septum, was charged with 1.1 g of "wet" W-2 type Raney-Ni

(taken from a suspension in aqueous NaOH of pH=11). The Raney-Ni was washed four times with absolute ethanol by cannula under nitrogen and dried under vacuum, resulting in 0.98 g of "dry" Raney-Ni. Absolute ethanol (10 mL) was added by syringe and to the resulting stirred suspension, a solution of **13a**/**13b** (6:4) (50 mg, 0.126 mmol) in 5 mL of absolute ethanol was added by syringe. The septum was replaced by a Dimroth condenser and the reaction mixture was refluxed under nitrogen for 12 h (monitoring by TLC). When conversion was complete, the system was cooled to room temperature and the alcoholic solution was filtered out by cannula. The Nickel powder was washed four times with ethanol in order to recover the adsorbed product. All alcoholic extracts were combined and concentrated to dryness, resulting in a crude oil, which was re-dissolved in ether and filtered through a pad of neutral alumina. Solvent was removed and product **14** (22.5 mg, 85% yield) was obtained as a colourless oil. IR (film) 3477 (O–H), 2930, 1452, 1379, 120, 1165, 1115 (C–O), 1024. ^{1}H NMR (500 MHz, $CDCl_3$) 0.97 (3H, s, H11), 1.39–1.48(1H, m, $H9_B$), 1.52–1.59 (2H, m, H4), 1.64 (3H, s, H12), 1.86-1.92 (3H, m, $H3_B$, H5), 1.95–2.0 (1H, m, $H8_B$), 2.02–2.08 (1H, m, $H9_A$), 2.28–2.35 (1H, m, $H8_A$), 2.37–2.46 (1H, m, $H3_A$), 3.38 (3H, s OMe), 3.69-3.74 (1H, m, H2), 4.00 (1H, dd, J_1=11.0 Hz, J_2=6.0 Hz, H10). ^{13}C NMR (75.43 MHz, $CDCl_3$) 15.3 (C12), 19.9 (C4), 23.1 (C11), 26.2 (C9), 27.7 (C10), 31.4 (C3), 34.0 (C5), 52.9 (C1), 57.8 (OMe), 70.7 (C6), 84.6 (C8), 130.7, 136.6 (C6, C7). COSY ^{1}H–^{1}H (500 MHz, $CDCl_3$): H2–$H3_B$, $H3_A$–$H3_B$, $H3_A$–H4, $H3_B$–H4, H4–H5, $H8_A$–$H8_B$, $H8_A$–$H9_A$, $H8_B$–$H9_B$, $H9_A$–$H9_B$, $H9_A$–H10, $H9_B$–H10. EM [DIP-CI-NH_3, 70 eV, 150°C, *m/z* (%)]: 210 (5, M), 211 (62, M+H), 212 (15, M+2H), 226 (12, M+16), 228 (M+NH_4), 245 (3, M+N_2H_5). EA Calculated for $C_{13}H_{22}O_2$: C (74.23%), H (10.55%). Found: C (74.30%), H (10.60%). $[\alpha]_D^{22}=-35°$ (1.5%, EtOH). GC (Type C conditions) t_R=17.60 min. TLC (SiO_2, hexane/ether 4:6) R_f=0.45.

Preparation of (1*R*,2*S*,6*S*,7*S*,10*R*)-1,6-dimethyl-10-methoxy-bicyclo[5.3.0]decan-2-ol, 15. To a suspension of 15 mg of Pd/C (10% w/w) in absolute MeOH, placed in a 25 mL flask, 40 mg (0.19 mmol) of **14**, dissolved in 5 mL of anhydrous MeOH, were added by syringe. The reaction vessel was pumped and back filled with hydrogen three times and the reaction mixture was vigorously stirred under hydrogen atmosphere (1 atm), at room temperature, for 2 h (control by GC). The organic solution was filtered out by cannula, and the portion of product adsorbed on catalyst was recovered by sonication of a re-suspension of the residual solid in MeOH. This operation was repeated three times. Solvent was taken out by rotatory evaporation, ether was added, and the ethereal solution was filtered through a short pad of neutral alumina, and concentrated to dryness, resulting in 36.2 mg (90% yield) of product **15** as a colourless oil. Product **15** is a 95:5 mixture (by GC) of diastereoisomers **15a** and **15b**, respectively. Isomer **15a** purified by flash column chromatography on silica gel, using mixtures of hexane/ether of increasing polarity as eluents. **15a** was isolated as a colourless oil, IR (film) 3467 (O–H), 2929, 2871, 1456, 1373, 1194 (C–O), 1119, 1059. ^{1}H NMR (200 MHz, $CDCl_3$) 0.85 (3H, s, H11), 0.87 (3H, d, *J*=6.6 Hz, H12), 1.22–1.70 (8H, m, H4, H5, H6, H7, H8), 1.75–2.05 (4H, m, H3, H9), 3.32 (3H, s, OMe), 3.79–3.86 (2H, m, H2, H10). ^{13}C NMR (75.43 MHz, $CDCl_3$) 12.6 (C12), 19.1 (C4), 22.2 (C11), 25.6, 26.5 (C5, C8), 34.3 (C9), 34.8 (C6), 35.9 (C3), 42.5 (C7), 49.9 (C1), 57.5 (OMe), 72.7 (C2), 83.9 (C10). EM [CG/EM, DIP-CI-NH_3, 70 eV, 150°C, *m/z* (%)]: 195 (50, M−17), 213 (90, M+H), 230 (100, M+NH_4). EA Calculated for $C_{13}H_{24}O_2$: C (73.52%), H (11.40%). Found: C (73.60%), H (11.38%). $[\alpha]_D^{22}=-16°$ (1%, EtOH). GC (Type C conditions) t_R=17.94 min. TLC (SiO_2, hexane/ether 4:6) R_f=0.33.

Preparation of (1*S*,6*S*,7*S*,10*R*)-1,6-dimethyl-10-methoxy-bicyclo[5.3.0]decan-2-one, 16. To a suspension of 73 mg (0.34 mmol) of pyridinium chlorochromate in 5 mL of anhydrous methylene chloride, was added, **15a** (40 mg, 0.19 mmol) was added, dissolved in 2 mL of anhydrous CH_2Cl_2. The reaction mixture was vigorously stirred under anhydrous conditions at room temperature for 2 h, turning from orange into dark brown. The resulting black gummy crude mixture was extracted with dry ether (3×20 mL), and the upper phase was decanted. The residue was re-suspended in ether and sonicated for 15 min three times. The combined ethereal solutions were passed through a short pad of neutral alumina and concentrated to dryness, resulting in 40 mg of an oily crude, which was submitted to flash column chromatography on silica gel, eluting with hexane/ether mixtures of increasing polarities. Product **16** (37.6 mg, 95% yield) was isolated as a colourless oil. IR (film) 2929, 1696 (C=O), 1456, 1375, 1124 (C–O). ^{1}H NMR (200 MHz, $CDCl_3$) 0.86 (3H, d, *J*=6.6 Hz, H12), 1.20 (3H, s, H11), 1.00–2.10 (10H, m, H4, H5, H6, H7, H8, H9), 2.50 (1H, m, H3), 2.72 (1H, m, H3), 3.27 (3H, s, OMe), 4.19 (1H, dd, J_1=8.0 Hz, J_2=8.5 Hz, H10). ^{13}C NMR (50 MHz, $CDCl_3$) 9.7 (C11), 21.2 (C12), 21.7 (C4), 25.6 (C8), 26.1 (C9), 35.8 (C6), 36.4 (C5), 41.6 (C3), 51.6 (C7), 57.7 (OMe), 59.5 (C1), 83.6 (C10), 214.9 (C2). EM [CG/EM, DIP-CI-NH_3, 70 eV, 150°C, *m/z* (%)]: 178 (2, M−MeOH), 195 (6, M−CH_3), 211 (100, M+H), 228 (62, M+NH_4). EA Calculated for $C_{13}H_{22}O_2$: C

Table 1. Crystal data and structure refinement for **10a**

Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$ (No. 19)
Unit cell dimensions	a=9.2187(11) Å, α=90°, b=9.962(2) Å, β=90°, c=13.728(2) Å, γ=90°
Volume	1260.7(3) Å^3
Z	4
Density (calculated)	1.266 Mg/m^3
Absorption coefficient	0.093 mm^{-1}
F(000)	520
Crystal size	0.84×0.61×0.38 mm
Theta range for data collection	2.66–28.29°
Index ranges	$-11\le h\le 12$, $-13\le k\le 13$, $-18\le l\le 18$
Reflections collected	13 494
Independent reflections	3103 [R(int)=0.0529]
Data/restraints/refined parameters	2969/0/215
Goodness-of-fit on F^2	1.049
Final R indices [$I>2\sigma(I)$]	$R1$=0.0448, $WR2$=0.1110
Extinction coefficient	0.143(10)
Absolute structure parameter	0.4(13)
Largest difference peak and hole	0.168 and −0.172 e Å^{-3}

Table 2. Selected bond lengths (Å) and angles (°) for **10a**[34]

Bond	Length (Å)	Bond	Angles (°)
C2′–O2′	1.204(3)	O1″–C1′–C2′	112.9(2)
C2′–C1′	1.534(2)	O1″–C1′–C2	107.77(14)
C1′–O1″	1.409(2)	C2′–C1′–C2	111.6(2)
C1′–C2	1.554(2)	C9–C2–C3	111.2(2)
O1″–C1″	1.421(3)	C9–C2–C1	111.0(2)
C2–C9	1.527(2)	C3–C2–C1	106.35(14)
C2–C3	1.536(3)	C9–C2–C1′	111.1(2)
C2–C1	1.549(2)	C3–C2–C1′	107.36(14)
C1–O8	1.434(3)	C1–C2–C1′	109.56(14)
C1–C7	1.525(2)	O8–C1–C7	103.4(2)
O8–C5	1.436(3)	O8–C1–C2	109.61(14)
C6–C7	1.533(3)	C7–C1–C2	113.6(2)
C5–C6	1.525(3)	O8–C5–C6	103.6(2)
C4–C5	1.539(3)	O8–C5–C4	108.49(14)
C3–C4	1.519(3)	C6–C5–C4	113.7(2)
C3–O3	1.208(2)	C3–C4–C5	107.9(2)

(74.23%), H (10.55%). Found: C (74.28%), H (10.48%). $[\alpha]_D^{22}=18°$ (1.2%, EtOH). GC (Type C conditions) $t_R=29.26$ min. TLC (SiO_2, hexane/ether 4:6) $R_f=0.41$.

X-Ray structure determination of 10a.[34] Data collection for **10a** was performed on a STOE IPDS apparatus. The crystal was rotated in 1.9° steps to yield 116 exposures and each of them was irradiated for 2.4 min. Intensity data were integrated using 200 control reflections and converted into a SHELX *hkl*-file with the STOE IPDS software (version 2.65). The input files for the SHELX programs were prepared with the program UTILITY.[35] Structure solution was performed with Direct Methods (SHELXS-86)[36] and subsequent difference-Fourier synthesis (SHELXL-93).[37] Refinement on F^2 was carried out by full-matrix least-squares techniques (SHELXL-93). Non hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were included using a riding model with $d_{CH}=0.96$ Å and $U=1.2U_{eq}$ of the preceding normal atom. Neutral atom scattering factors were taken from Cromer and Mann.[38] Illustrations were performed with Zortep.[39] In the final stages of refinement, data were corrected for extinction effects. The absolute structure could not be determined. The Flack[40] Parameter of 0.4(13) indicated no preference for one special configuration. There was no difference in the *R*-values and Goodness of Fit upon refinement of the structure with the converted atomic co-ordinates. Also a Twin refinement was employed to test the absolute structure without any changes in the results (see Tables 1 and 2).

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34. Supplementary material available. Complete crystal data, list of refined coordinates and a complete list of bond distances are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this work. See *Tetrahedron* **1984**, *40*, 2, ii.

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