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Versatile Methodology to Synthesize Oxygen-Bridged Nine- and Ten-Membered Cycloalkanes by the Hypoiodite Reaction

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C-3 derivatives of 6-hydroxy-2,7-dimethyl-11-oxatricyclo[6.2.1.0^{2,6}]undecan-4-one reacted with lead tetraacetate (LTA) and iodine to afford, in good yield, 1,7-epoxycyclononanes, which are the result of a β-fragmentation of the C2–C6 bond adjacent to the tertiary hydroxy group on C-6. This β-fragmentation is followed by a ring contraction from a ten- to a nine-membered ring system, by a free-radical addition to the carbonyl group on C-4. The reaction of precursors (not functionalized on C-3) with LTA and iodine produced a β-fragmentation without any further structural rearrangement, affording 1,8-epoxycyclodecanes. The transformation of the carbonyl group on C-4 to acetate avoided radical additions and rearrangements affording, in high yield, the corresponding cyclodecanes. By this methodology, either 1,7-epoxycyclononane or 1,8-epoxycyclodecane could be synthesized, in good yield, by choosing the appropriate substitution pattern on C-3 in the substrate.

Introduction

The 1,8-epoxycyclodecane systems are structural units which are present in a wide range of terpenoids. Most of these natural products present interesting pharmacological activities like the well-known eleutherobin[1] (Figure 1), which possesses antitumor properties closely related to those of paclitaxel. Other examples of bioactive natural products having this oxabicyclic framework worth noting are goiazensolides,[2] which are secondary metabolites of plants, and sclerophytins[3] and other antineoplasic diterpenic cembranoids of marine origin, found in soft corals (Figure 1). Bioactive products containing the 1,8-epoxycyclodecane framework have a growing interest among synthetic chemists and several total syntheses of this type of molecules have been described.[4]

On the other hand, the 1,7-epoxycyclononane framework is considerably less widespread than its 1,8-epoxycyclodecane homologue among natural products; however, a few examples of interesting compounds containing this oxabicyclic framework appear in the literature.[5] Worth noting are the physalins[6] (Figure 2), a large family of natural *seco*-steroids with a wide range of biological activities. Physalins are natural products isolated from different species of *Physalis solanaceae*, abundant on the American continent.[7] These compounds have an important cytotoxic activity which has generated a special interest among the scientific community.

In this context, several methodologies have appeared in the literature to synthesize the oxabicyclic frameworks of 1,8-epoxycyclodecane and 1,7-epoxycyclononane (i.e. 11-oxabicyclo[6.2.1]undecane and 10-oxabicyclo[5.2.1]decane). Many of these methodologies only can be used for a certain type of substrate or they are not compatible with some functional groups. For these reasons it is necessary to consider all possible synthetic solutions to face the synthetic and structural challenges represented by the aforementioned target molecules. Among these synthetic methodologies are worth noting the following: (a) 1,4-elimination reactions mediated by a base in the presence of a good leaving group[8] (this is a kind of Grob fragmentation[9] that affords good results if the disposition of the hydrogen atom to be abstracted and the leaving group are adequate), (b) retroaldol reactions,[10] (c) cyclobutane thermolysis by a [2+2] cycloreversion reaction,[11] (d) transannular ring expansion induced by electrophiles,[12] (e) transannular cyclization in acidic media,[13] (f) ring expansion mediated by hydrogen peroxide,[14] (g) intramolecular reductive coupling mediated by SmI_2,[15] (h) anionic oxy-Cope rearrangement[16] (this reaction is less reversible than the conventional Cope re-

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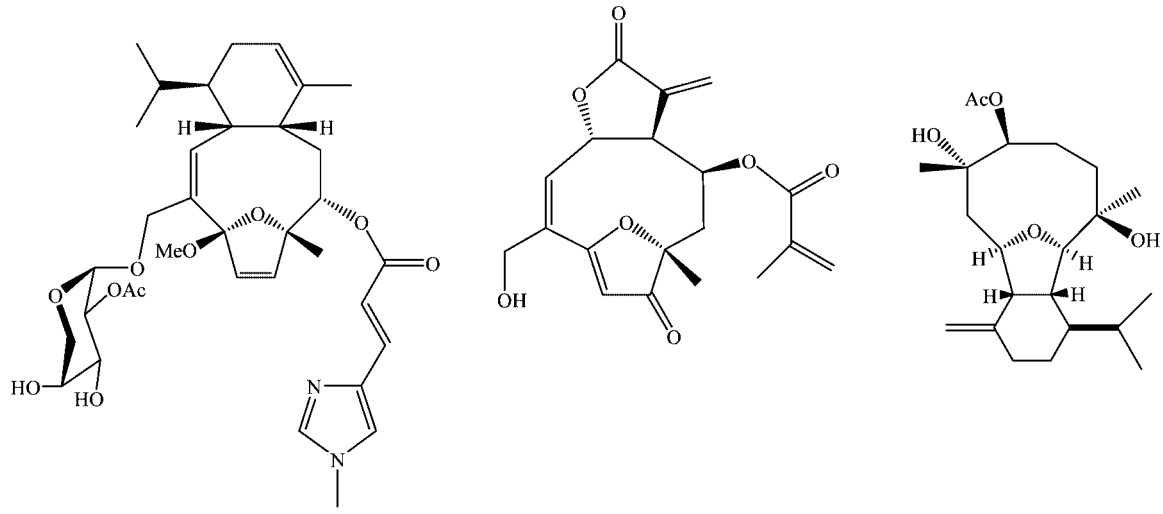


Figure 1. Examples of 1,8-epoxycyclodecanes with antitumour activity.

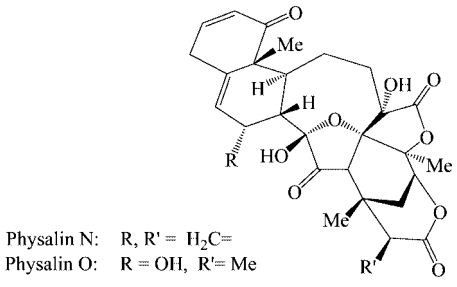
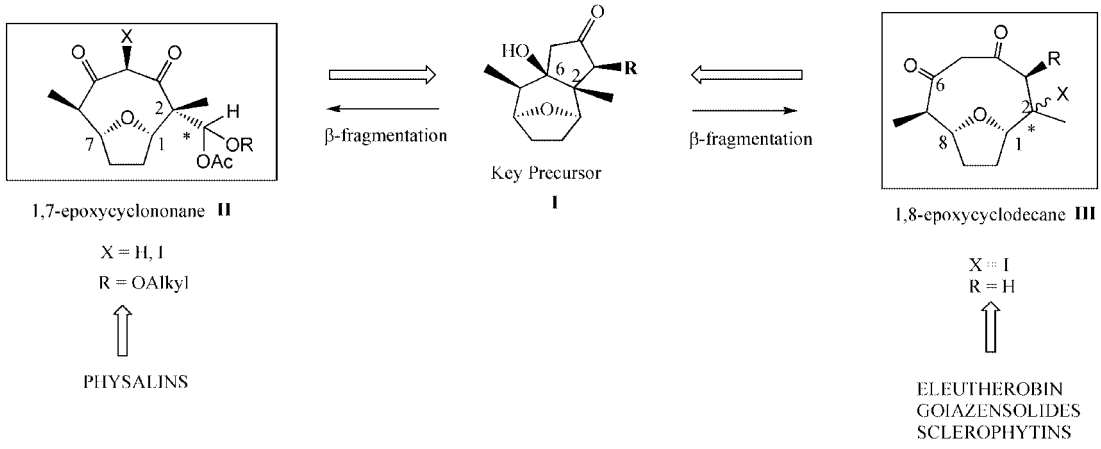


Figure 2. Examples of physalins with cytotoxic activity.

arrangement because the initially formed enol tautomerises to afford the corresponding ketone), and (i) the hypoiodite reaction.[17]

In the present work, a new methodology to synthesize 1,7-epoxycyclononane and 1,8-epoxycyclodecane systems is reported. Also, interesting structural and mechanistic aspects are included, which involve the contraction of a ten-membered ring into a nine-membered ring, by an intramolecular free-radical addition to a carbonyl group. Moreover, it is reported how the modification of the substrate by a carbonyl group transformation into a protected alcohol (in order to avoid free radical additions and rearrangements) afforded, in high yield, the corresponding 1,8-epoxycyclodecanes. Thus, by this methodology, either 1,7-epoxycyclononane or 1,8-epoxycyclodecane could be synthesized in good yield from a versatile precursor.

The main objective of the present work was to develop a synthetic methodology in order to prepare a selected library of potential antitumor compounds, analogues of the aforementioned bioactive natural products, containing the 1,7-epoxyxyclononane and 1,8-epoxycyclodecane frameworks, with the purpose of carrying out structure-activity relationship studies. To reach this objective, compound **I** was considered a key versatile precursor, from the retrosynthetic point of view, to the target molecules **II** and **III** (Scheme 1). In a first approach, these oxatricyclic starting materials **I** could be transformed into the desired 1,7-epoxycyclononanes, precursors of physalins, and 1,8-epoxycyclo-



Scheme 1. Key oxatricyclic precursor **I** to generate 1,7-epoxycyclononanes (**II**) and 1,8-epoxycyclodecanes (**III**) by β-fragmentation reactions.

decanes, precursors of eleutherobin, goiazensólides and sclerophytins by a β-fragmentation of the C2–C6 bond (Scheme 1).

Results and Discussion

Synthesis of Key Precursors 16–18

We have developed a synthetic methodology to construct 11-oxatricyclo[6.2.1.$0^{2,6}$]decane skeletons (**I**), conveniently functionalized. We report here the application of this synthetic strategy to the preparation of oxamacrobicycles which are the framework of the aforementioned large family of natural products with important biological activities. It is a methodology based on two key reactions: (1) a [4+3] cycloaddition[18] [to generate the seven-membered ring (see Scheme 2)] and (2) the Nicholas reaction,[19] to electrophilically insert the propargyl entity which will, in turn, facilitate the construction of the five-membered ring by an intramolecular cyclization (Scheme 2).

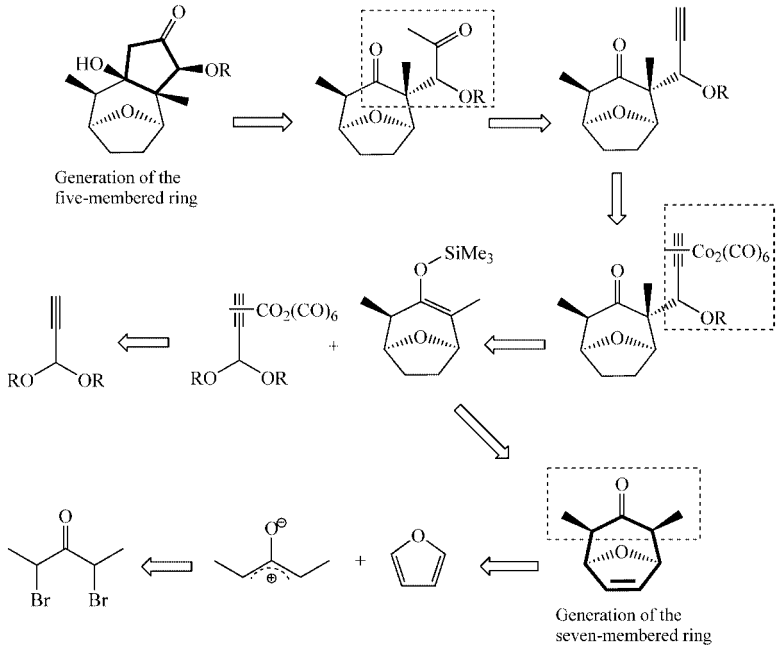
Moreover, it is a versatile synthetic strategy, because by choosing an adequate substitution pattern in the propargyl, furan and dihalo ketone (for preparation of the 2-oxyallyl cation) precursors it is possible to prepare a wide range of related structures. An active effort in this research field has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

The cycloheptane moiety of our bicyclic system was prepared by a [4C(4π)+3C(2π)] cycloaddition reaction between furan (**3**) and 1,3-dimethyl-2-oxyallyl cation (Scheme 2), generated in situ by the reduction of 2,4-dibromo-3-pentanone (**2**) with Cu/NaI at 55 °C.[20] This reaction afforded a mixture of diastereomers **4a/4b** (*cis*-diequatorial/*cis*-diaxial) in an 80:20 ratio and in 95% yield (Scheme 3).[21]

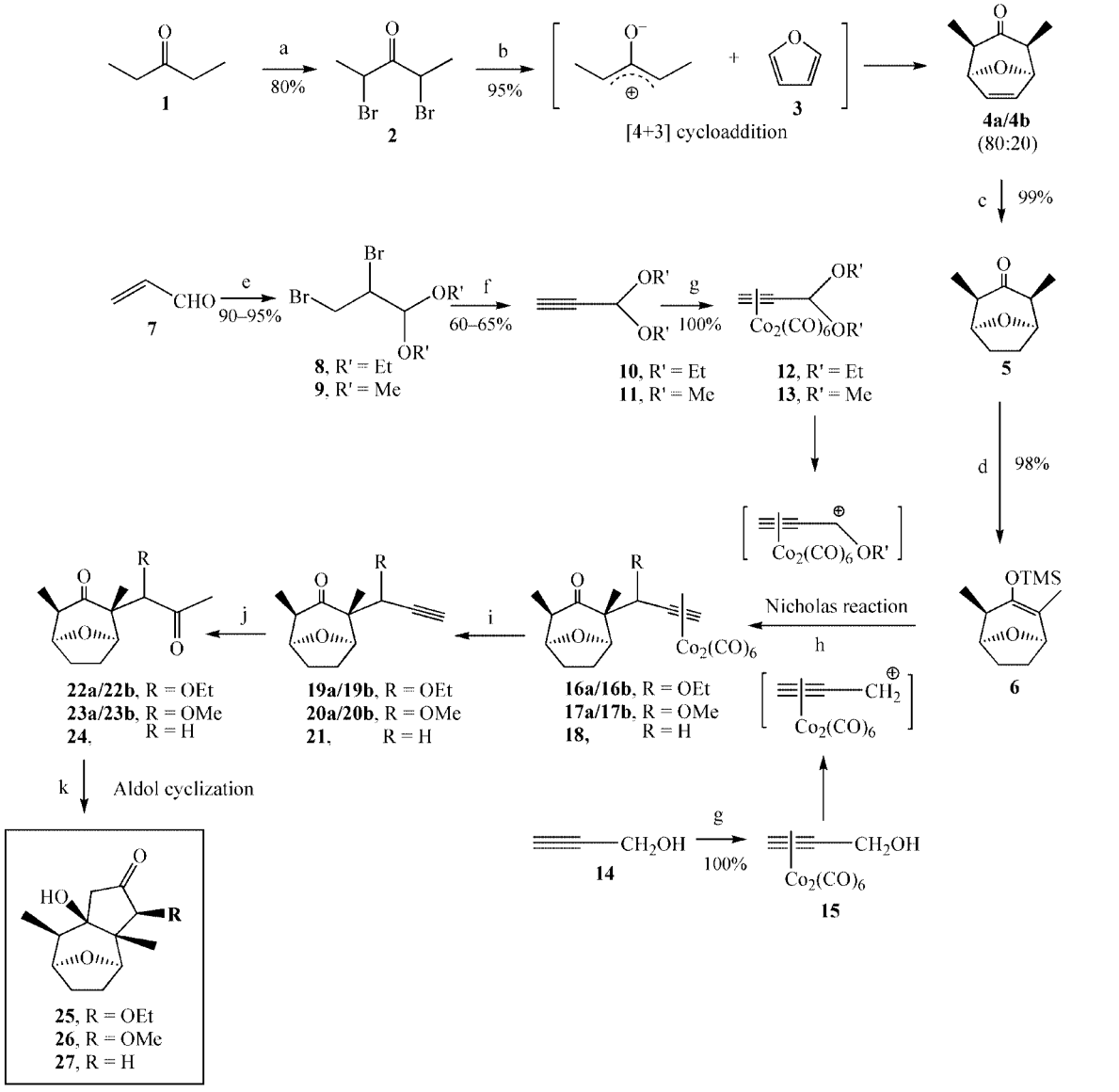
The major diastereomer **4a** has both methyl groups in a diequatorial disposition for a boat-like conformation of the 1-oxan-4-one ring, and it is easily separable from **4b** by column chromatography. Halo ketone **2** was obtained in 80% yield by bromination of cheap and commercially available 3-pentanone (**1**) under acid catalysis.[20] Catalytic hydrogenation of the C6–C7 double bond afforded in quantitative yield the cycloheptanone **5**.

The oxabicycle **5** was efficiently converted into the silyl enol ether **6**, in 98% yield, by its treatment at –78 °C with LDA followed by the quenching of the formed enolate with trimethylsilyl chloride (>99% pure), under extremely anhydrous conditions. This methodology can be applied in an enantioselective manner by using a chiral base,[22] instead of LDA, which allows the desymmetrisation of the *meso*-oxabicycle **5** in an early stage of the synthetic pathway.

The three-carbon subunit, necessary to assemble the five-membered ring of the 11-oxabicyclo[6.2.1.$0^{2,6}$]decane system, was introduced by an electrophilic attack of the propargyl cations (stabilized as hexacarbonyldicobalt complexes) on silyl enol ether **6** (Nicholas reaction).[19] These propargyl cations were generated in situ from cobalt complexes **12**, **13** and **15** by reaction with $BF_3{\cdot}OEt_2$.[23] Cobalt complexes **12** and **13** were prepared, in quantitative yield, from the precursory acetylenic acetals **10** and **11**, respectively, which were readily obtained from acrolein[20,24] (see Scheme 3). The preparation of cobalt complex **15** was straightforward, starting from propargyl alcohol (**14**, see Scheme 3). The Nicholas propargylation of **6** produced in high yield a 1:1 diastereomeric mixture of **16a/16b** and **17a/17b**, which are pairs of epimers at C-1′, starting from cobalt complexes **12** and **13**, respectively. Also, propargylation product **18** was obtained from the reaction of cobalt com-

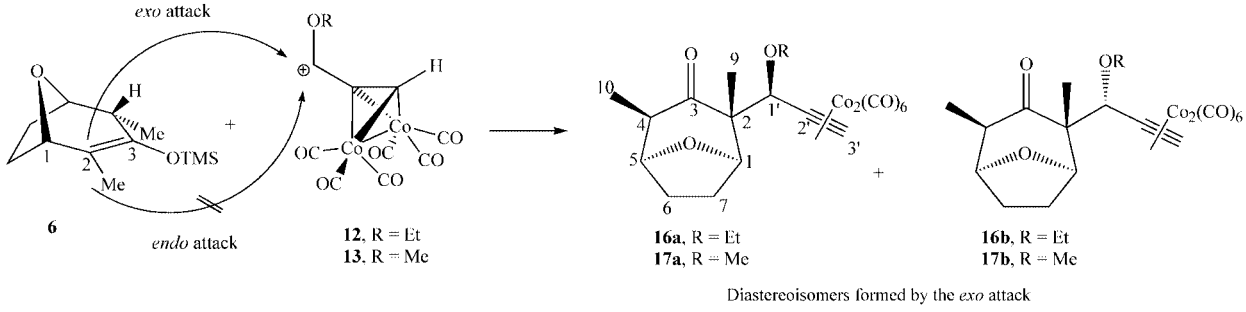


Scheme 2. Retrosynthesis of the five- and seven-membered rings of the bicyclo[5.3.0]decane framework.



Scheme 3. Synthetic methodology to prepare substrates **25**, **26** and **27**. (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, room temp.; (d) LDA, –78 °C, THF, then TMSCl; (e) Br_2, then $HC(OMe)_3$ in MeOH or $HC(OEt)_3$ in EtOH, 0–5 °C; (f) NaOH, Bu_4NHSO_4, H_2O/Et_2O, room temp.; (g) $Co_2(CO)_8$, pentane, room temp.; (h) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C; (i) CAN, Et_3N, acetone, 0 °C; (j) Hg^{II} *p*-toluenesulfamidate, $EtOH/H_2O$ (85:15), reflux; (k) anh. KOH, abs. EtOH, room temp. For yields of steps h–k see Table 1.

plex **15** (see Scheme 4 and Table 1). The epimeric ratio (**a**/**b**) 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 diastereomers could be theoretically possible as products. However, due to the



Scheme 4. Preferential attack of the hexacarbonyldicobalt(propargylium) cation by the *exo* face of the π-system of silyl enol ether **6**.

Table 1. Reaction outcome and yields of the Nicholas reaction, demetallation of cobalt complexes, hydration of acetylenes and aldol cyclization of methyl ketones in the synthesis of substrates **25**, **26** and **27**.

R	Substrate	Products and yields [%][a]							
		Step h: Nicholas reaction[b]		Step i: demetallation[c]		Step j: triple bond hydration		Step k: aldol cyclization[d]	
OEt	**12**	**16a/16b**	75–79	**19a/19b**	80–84	**22a/22b**	80–85	**25**	80–95
OMe	**13**	**17a/17b**	70–98	**20a/20b**	71–94	**23a/23b**	80–85	**26**	78–80
H	**15**	**18**	95–98	**21**	90–95	**24**	70–86	**27**	75–78

[a] The range of yields was obtained from five different trials for each substrate. [b] The yield in this step depends on both the reaction time and the work scale. [c] In this step the variation of yields depends on the type of workup. [d] The yield depends on the reaction time. Conversion was not complete in most cases.

bulkiness of the organocobalt cluster, the attack of the prochiral propargylium cation is only possible by the *exo* face of silyl enol ether **6**, forming only two diastereomers (see Scheme 4).

Compounds **16a** and **16b** or **17a** and **17b** were separated by column chromatography for their physical and spectroscopic characterization, but for synthetic purposes both of them were allowed to react as a mixture. In Table 1 the yields are quoted for the different trials of this reaction. We have observed that, for the same molar ratio among reagents, when increasing the reaction time beyond 2 h the yield decreases. On the other hand, when increasing the scale of work the yield also increased.

The cobalt complexes **16a/16b**, **17a/17b** and **18** were demetallated with cerium(IV) ammonium nitrate (CAN) and NEt_3 in acetone affording acetylenes **19a/19b**, **21b/20b** and **21** in good yield (see Table 1). Under these conditions both pairs of epimers were configurationally stable and the ratio among acetylenes was identical to that of the complexes. In the next step, the pairs of epimers **19a/19b** and/or **21b/20b** were allowed to react as mixtures, but for their characterization the individual compounds were also separated and purified by column chromatography. If Nicholas coupling and demetallation reactions were carried out in one pot the overall yield of both steps could be improved by 10%.[23] It is worth noting that the type of workup in the demetallation process may influence the yield of the resulting acetylene. The typical workup that involves the addition of water to the reaction mixture and extraction with diethyl ether is the one that affords the worst results due to the formation of thick emulsions, induced by cobalt or cerium salts. Centrifugation of these emulsions improves the results of the isolation of the products. We have found a much better alternative in the direct filtration of the crude reaction mixture through a three-layer short pad of Celite®, alumina, and silica gel, in this order and eluting with acetone. All the cobalt salts and most of the cerium salts are retained in this way. The yield of demetallated product after this workup protocol was improved by 50% relative to those of the previous procedure.

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.[25] These reaction conditions afforded in our case a low yield of products and propitiated polymerization of acetylenes and epimerization of stereocentres, by the enolization of ketones, among other side processes. To avoid this problem, the hydration of the triple bond was performed under neutral conditions[26] by using Hg^{II} *p*-toluenesulfonamidate to afford diketones **22a/22b** (1:1), **23a/23b** (1:1) and **24** in good yield (see Table 1). Under these conditions, the epimeric pairs of methyl ketones were configurationally stable and no modification of stereocentres at C-4 and C-1′ was observed. This behaviour was confirmed by performing the hydration reaction on separated acetylenes **20a** and **20b** and obtaining in each case only one product **23a** and **23b**, respectively.

The aldol cyclization of methyl ketones **22a/22b**, **23a/23b** and **24** by using anhydrous KOH in absolute ethanol formed oxatricyclic compounds **25**, **26** and **27**, respectively, in high yield (see Table 1), as a unique product. It is worth noting that this aldol reaction is stereo-convergent and both epimers gave the same final products: **22a** and **22b** afforded **25**, **23a** and **23b** formed **26**, and **24** generated **27**. This phenomenon could probably take place through a keto-enol equilibrium involving precursor methyl ketone **23b**, which could epimerize to **23a** and/or at the level of the aldol intermediate, to evolve to a more stable Me–C-2 vs. R′O–C-3 *trans* relationship. To evaluate both possibilities we carried out the aldol reaction on both epimers **23a** and **23b** separately, stopping the reaction at 50% conversion of substrate, in order to detect possible intermediates. In the case of the reaction of **23a** we exclusively observed unchanged **23a** and aldol **26**. On the other hand, in the reaction mixture coming from **23b** we observed unreacted **23b** (8%), its epimer **23a** (42%) and product **26** (50%). According to these findings both keto-enol equilibria are responsible for this interesting thermodynamically driven stereo-convergence. According to these studies we can conclude that long reaction times are necessary (24 h) to reach a complete conversion and a high degree of isomerization, by enolisation, in order to convert all possible aldols into the thermodynamically most stable stereoisomer. If shorter reaction times are used a certain percentage of other isomers, epimers at C-3 or C-7, were observed.

β-Fragmentation Reactions

The desired C2–C6 fragmentation in the substrates **25**, **26** and **27** could be accomplished by using several oxidizing agents[27–32] such as CAN, lead tetraacetate (LTA) or by the

use of the hypoiodite reaction conditions[17,33] in the presence of the tandem reagents HgO/I_2 and/or LTA/I_2 among others.[33a,33c] All the aforementioned reagents were evaluated under several reaction conditions and the system LTA/I_2 showed to be the most efficient one for our substrates, resulting in shorter reaction times and higher yields than with the other alternatives. Thus, substrates **25** and **26** were dissolved in anhydrous benzene and treated with LTA and iodine in a 3:1 molar ratio, submitting the mixture to irradiation with two 100 W lamps. After workup, the crude mixture was fractionated by column chromatography on silica gel and four compounds were separated, which were physically and spectroscopically characterized (^1H NMR, ^{13}C NMR, DEPT, COSY, HETCOR, IR, MS and EA). From substrate **25** two pairs of reaction products were isolated and identified: the iodinated compounds **28a** and **28b**, epimers of each other, and the non-iodinated products **29a** and **29b**, which are also epimers of each other at the asymmetric acetal carbon atom. In a similar way, from substrate **26** four compounds were isolated: the iodinated epimers **30a** and **30b** and the non-halogenated epimers **31a** and **31b** (see Table 2).

The reaction of substrate **25** with LTA/I_2 under milder conditions (using a 1:1:1 molar ratio of substrate/LTA/I_2) at room temperature (without 100 W lamp irradiation) for 2 h, afforded the non-iodinated aldehyde **32** as the major product in a 50% yield (see Table 2). Compound **32** was characterized and its structure confirmed by X-ray diffraction analysis (Figure 4).

Different parameters and reaction conditions were modified in order to understand and to optimize the β-fragmentation reaction. Thus, the reactivity of **27** was studied by

Table 2. Products resulting from the β-fragmentation of substrates **25** and **26**.

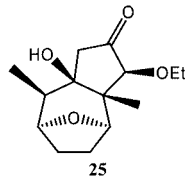
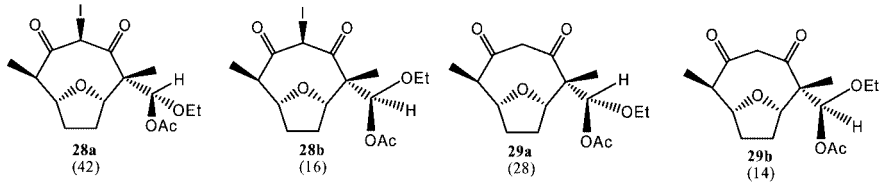
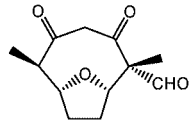
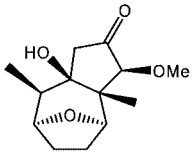
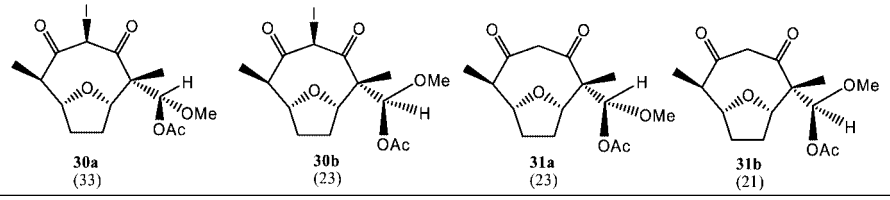
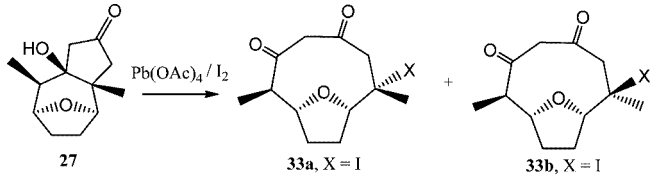
Substrate	Reaction conditions	Products (yield, %)
 **25**	LTA/I_2 (3:1) hv, 45 °C, 2 h benzene	 **28a** (42) **28b** (16) **29a** (28) **29b** (14)
	LTA/I_2 (1:1) r.t., 2 h benzene	 **32** (50)
 **26**	LTA/I_2 (3:1) hv, 45 °C, 2 h benzene	 **30a** (33) **30b** (23) **31a** (23) **31b** (21)

Table 3. Results from the reaction of **27** with LTA/I_2.



Trial	Molar ratio Substrate/LTA/I_2	Scale [mg]	hv[a]	T [°C]	t [h]	Yield [%]	Conversion [%]	Product ratio I/acetate derivatives **33a**,**b**/**34a**,**b**	**33a/33b**
1	1:3:1	100	yes	45	1	41	100	43:57	1:1
2	1:3:1	100	no	20	1	50	84	100:0	1:1
3	1:1:1	100	no	20	0.5	67	82	100:0	7:3
4	1:1:1	200	no	20	0.5	76	82	100:0	7:3
5	1:1:1	200	no	20	1	68	83	100:0	45:55
6	1:1:1	200	no	20	2	60	87	100:0	1:1

[a] Irradiation with two 100 W lamps.

performing different trials in which the following experimental conditions were modified: reaction temperature and time, use or not of two 100 W lamps (to induce radical formation) and the number of equiv. of LTA and iodine. The first three trials were performed using small amounts of **27** (100 mg); however, trials 4 and 5 were run on a larger scale (200 mg) in order to know the influence of the scale-up on the outcome and yield of the reaction. The results and conditions of these reactions are quoted in Table 3.

The first important observation from Table 3 was that in all products **33a**,**b** and **34a**,**b** a 1,8-epoxycyclodecane skeleton was present. The use of high molar ratios of LTA/substrate gave low yields of the desired products. Moreover, in order to obtain good selectivity it was preferable to work under milder conditions, even though the conversion was not complete, because the starting material could be recovered (trials 3–5 in Table 3). Increasing the scale of work slightly increased the yield, and shorter reaction times propitiated the formation of a higher proportion of epimer **33a** vs. **33b** (see trials 3 and 4 vs. 1, 2 and 5 in Table 3). Only in trial 1, performed at a high molar ratio of oxidizing agent, with heating and simultaneous irradiation with two 100 W lamps, was it possible to observe the formation of a pair of epimeric acetoxy derivatives **34a**,**b** together with the analogous iodinated cyclodecane products **33a**,**b**. When increasing the reaction time, maintaining constant the other reaction parameters (see Table 3, trials 4, 5 and 6), a higher conversion was observed but the reaction yield was not improved.

Assignment of the Relative Stereochemistry in the β-Fragmentation Products

The skeleton and functionality of **33a** and **33b** were established by a careful comparative study of the spectroscopic data (^{1}H NMR, ^{13}C NMR, IR and MS). The relative stereochemistry in both compounds was determined by a careful correlation of ^{1}H and ^{13}C NMR spectroscopic data according to the following protocol:

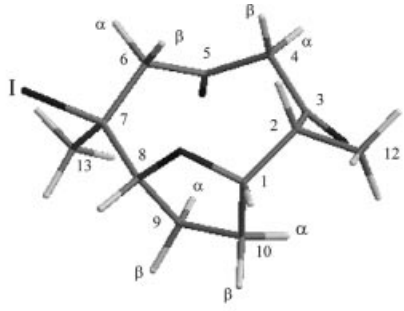
(a) Unequivocal assignment of the ^{1}H and ^{13}C NMR signals by 2D experiments (g-COSY, HETCOR, HMBC, HMQC and NOESY).

(b) Conformational analysis by MM2, MOPAC, and GAUSSIAN computational methods in order to know the minimum energy conformers for **33a** and/or **33b** that have the highest weighed contribution to observed δ (ppm) and J (Hz) values in solution.

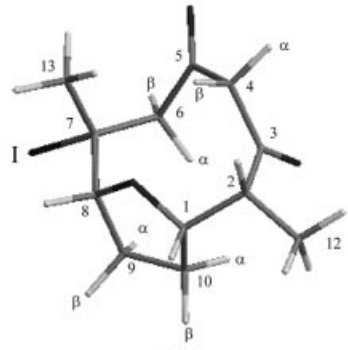
(c) Comparative study of the NMR spectroscopic data from all diastereomers. Analysis of significant differences and correlation studies. $\Delta\delta$ ($\delta_{33a} - \delta_{33b}$) was calculated (see Table 4) to know what structural changes would induce the main differences in chemical shifts between epimers at C-7. Thus, it was possible to understand how changes in the configuration at the C-7 stereocenter or how modifications in the conformation of the larger ring of the bicyclic system should determine the $\Delta\delta$ values observed for ^{1}H and ^{13}C NMR spectroscopic data.

(d) Study of the configuration-dependent stereoelectronic effects responsible for the significant and diagnostic ΔJ

Table 4. ^{1}H NMR and ^{13}C NMR correlation studies for **33a** and **33b**; δ values in ppm.



33a



33b

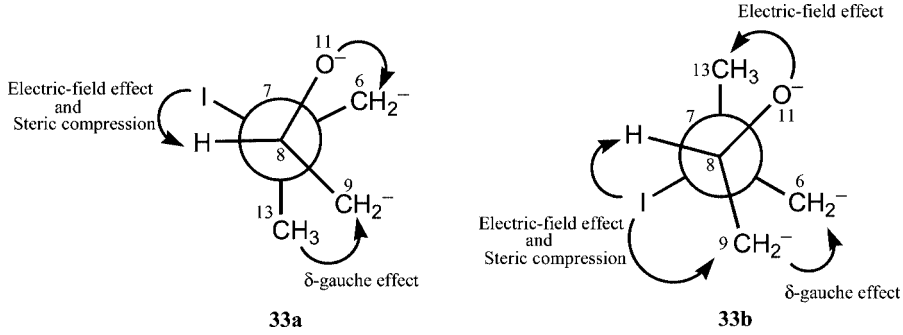
Proton	δ_{33a}	δ_{33b}	$\Delta\delta$ ($\delta_{33a} - \delta_{33b}$)	Carbon	δ_{33a}	δ_{33b}	$\Delta\delta$ ($\delta_{33a} - \delta_{33b}$)
1	4.30	4.37	–0.07	1	82.82	88.74	–5.92
2	3.48	3.35	0.13	2	47.99	47.89	0.10
4α	3.40	3.42	–0.02	3	209.70	209.46	0.24
4β	3.84	3.59	0.25	4	67.20	66.98	0.22
6α	2.55	2.72	–0.17	5	197.65	197.93	–0.28
6β	2.76	3.59	–0.83	6	48.66	50.38	–1.72
8	4.48	4.23	0.25	7	44.23	46.79	–2.56
9α	1.45	2.25	–0.80	8	91.59	85.70	5.89
9β	1.78	1.82	–0.04	9	25.99	32.03	–6.04
10α	2.30	2.25	0.05	10	25.68	25.04	0.64
10β	2.00	1.97	0.03	12	12.58	12.89	–0.31
12	0.97	0.96	0.01	13	35.04	35.50	–0.46
13	1.99	2.35	–0.6	–	–	–	–

(Hz) and $\Delta\delta$ (ppm) variations among diastereomers in their minimum-energy conformations.

(e) Assignment of the relative stereochemistry that should be consistent with all data and observations from the previous studies.

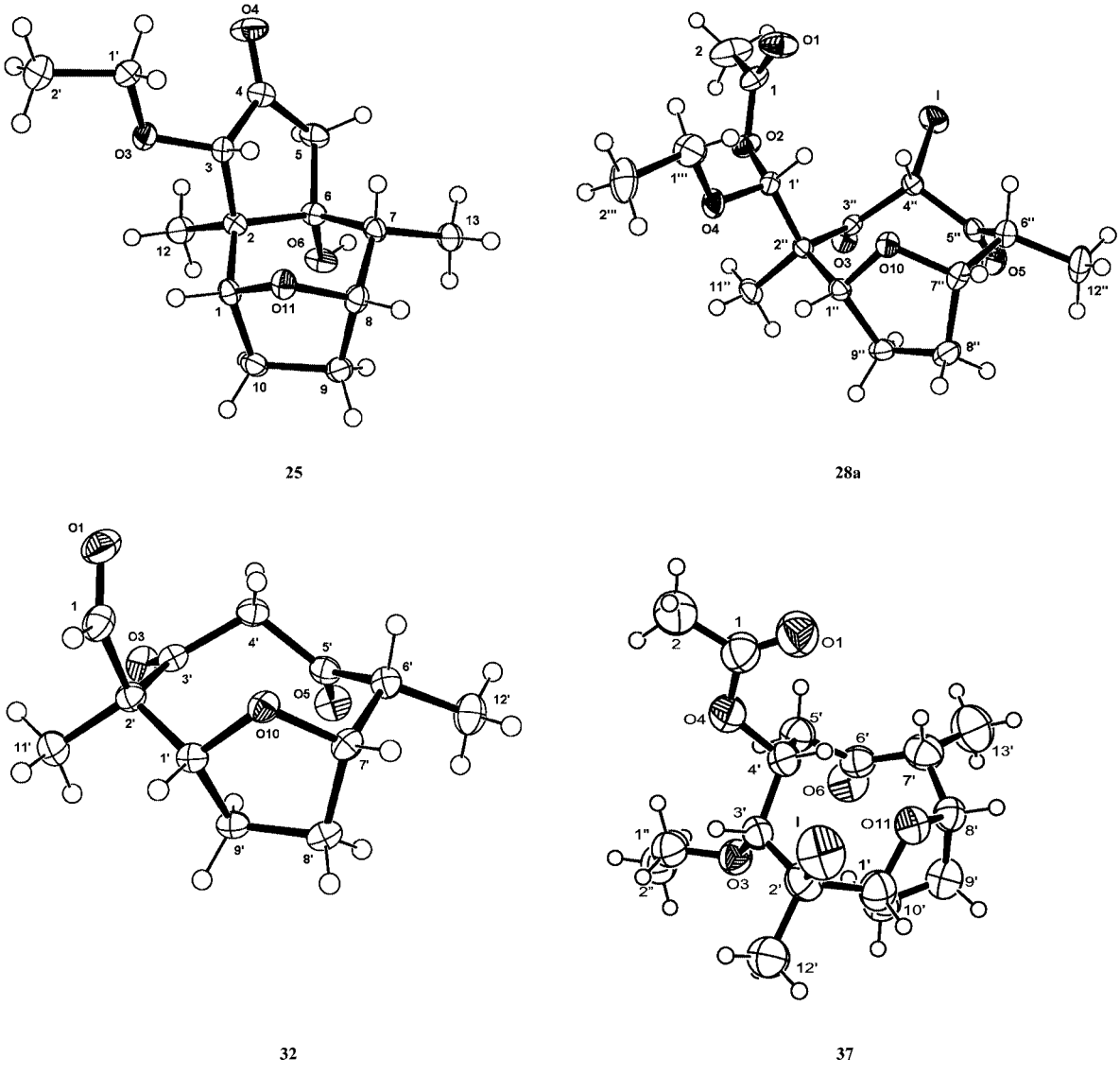
(f) Confirmation of the validity of the previous stereochemical assignments by X-ray diffraction analysis on single crystals of certain key products.

The main differences were observed in the chemical shifts of 4β-H ($\Delta\delta$ = 0.25 ppm), 6β-H ($\Delta\delta$ = –0.83 ppm), 8-H ($\Delta\delta$



33a **33b**

Figure 3. Physical interactions that explain the ^{1}H and ^{13}C NMR chemical shift differences between **33a** and **33b**.



25 **28a**

32 **37**

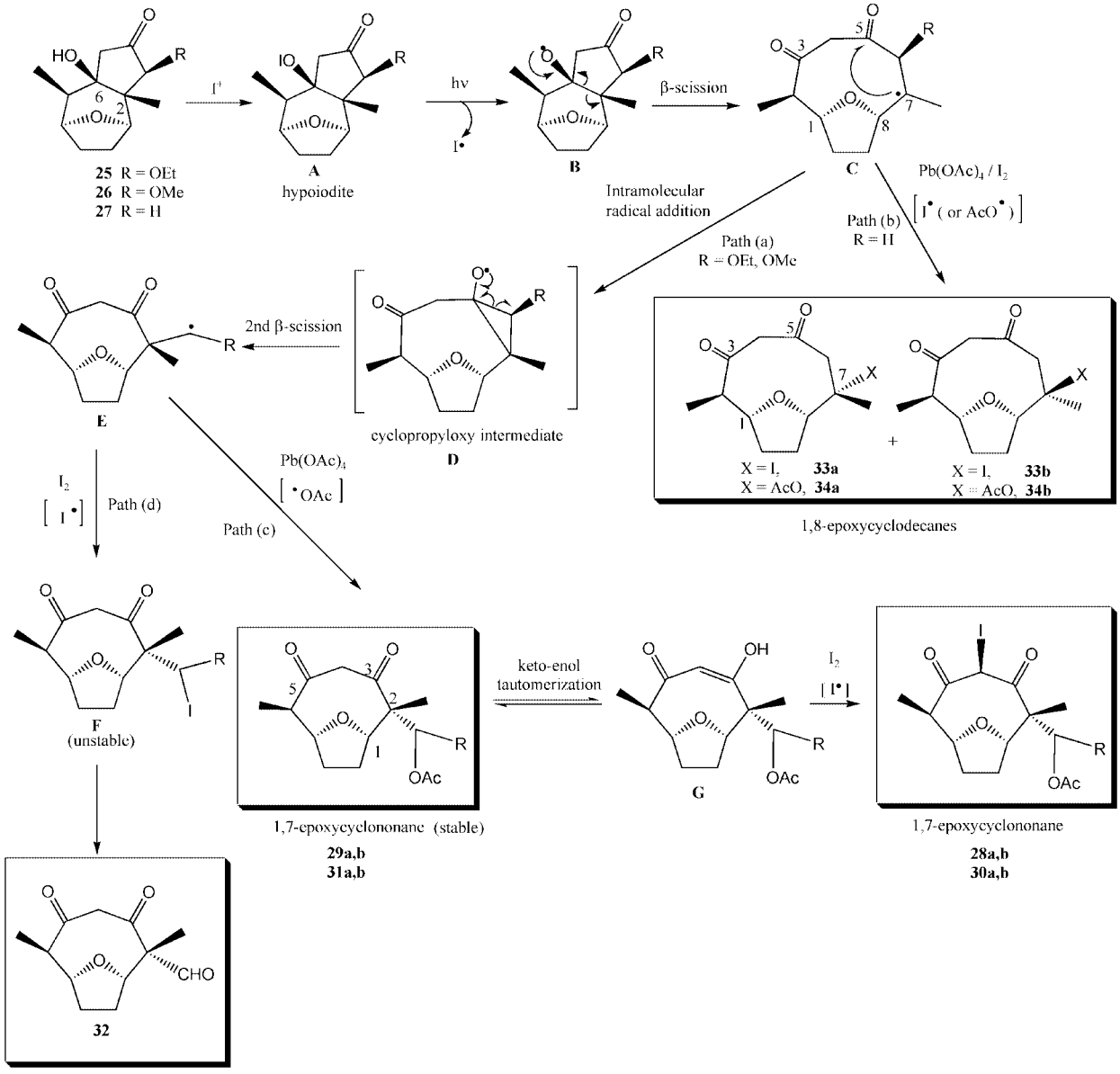
Figure 4. X-ray ORTEP figures with IUPAC numbering of compounds **25**, **28a**, **32** and **37**.

= 0.25 ppm), 9α-H ($\Delta\delta$ = –0.80 ppm) and 13-H ($\Delta\delta$ = –0.36 ppm). On the other hand, the largest differences in ^{13}C chemical shifts were observed for C-1, C-7, C-8 and C-9, with $\Delta\delta$ values of –5.92, –2.56, 5.89 and –6.04 ppm, respectively. All these chemical shift differences were produced by the following main physical phenomena[34,35] (see Figure 3): (a) The concomitant δ-gauche shielding effect[35a,36] between Me–C-7 and 9-H and the deshielding effect exerted by iodine on 8-H in **33a** by steric compression[35a,35c,36] and electric-field[35a,36a,36c] interaction and (b) the deshielding effect produced in **33b** by the bridging oxygen atom on 13-H_3 by a linear electric-field effect and the deshielding effect exerted by the iodine atom on 9-H by both a steric compression (responsible for the pull-push electron-density shift) and an electric-field interaction.

The protocol described above has been successfully applied to the **28a**,**b**, **29a**,**b**, **30a**,**b** and **31a**,**b** series of diastereomers and the assignment of stereochemistry has been confirmed by X-ray diffraction analysis in the case of **25**, **28a**, **32** and **37** (see Figure 4 and Table 6. See also Tables S1 and S2 of the Supporting Information).

Mechanistic Studies

The before-mentioned results could be interpreted on the basis of the following proposed mechanism. In this mechanism, the hypoiodite reaction[17] is a key step in which the free tertiary alcohol of **27** reacts with an iodonium cation, generated in situ from LTA and iodine, and forms the corresponding hypoiodite **A** (see Scheme 5). Subsequently, with the help of light and/or heating, the molecule undergoes a homolytic breakdown of the O–I bond, forming an alkoxy radical and releasing an iodine radical. This alkoxy radical undergoes a β-fragmentation[29] by a homolytic scission of



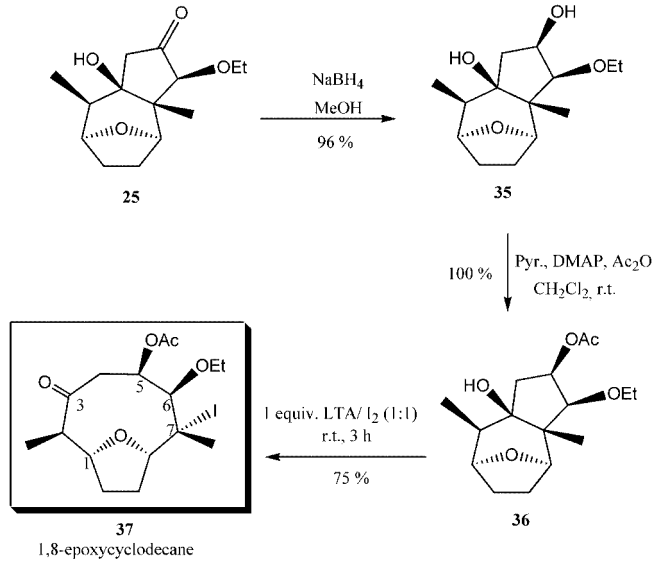
Scheme 5. Proposal of a formation mechanism of 1,7-epoxycyclononanes and 1,8-epoxycyclodecanes from substrates **25**, **26** and **27**.

the C2–C6 bond and a new carbon radical on position C-7 of intermediate **C** is formed. This last secondary radical reacts, by a radical termination reaction, with the previously released iodine radical to generate the neutral epimeric compounds **33a** and **33b** (path b, Scheme 5), in a stereoselective manner, depending on the reaction time (see Table 3). In a similar way (path b), the acetoxy derivatives **34a** and **34b** could be formed (see trial 1 in Table 3).

It is worth noting the difference in reactivity between substrates **25**, **26** and **27**. The only structural difference between these compounds is the absence of the alkoxy substituent in compound **27**. According to the obtained results, when precursors **25** and **26** reacted with LTA and I_2 in a 3:1 ratio or in a 1:1 ratio, they underwent a β-fragmentation with a structural rearrangement to a nine-membered ring system. On the other hand, when compound **27** was treated with LTA and I_2 in a 1:1 or 3:1 molar ratio, the expected ten-membered ring was generated in good yield. To explain the ring contraction undergone by the substrates **25** and **26**, it seems reasonable to suggest that the formation of the free radical **C** on C-7 should be followed by its attack and addition to the ketone carbonyl group at C-5 (path a, Scheme 5).[37] The intermediate cyclopropyloxy free radical **D** then undergoes a β-scission to afford the cyclononane ring. The new secondary radical **E** (Scheme 5) could subsequently react with an acetoxy free radical, generated from the photodecomposition of LTA, following path (c) to give the non-iodinated diketone (**29a**, **29b**, **31a**, or **31b**). The iodo derivatives (**28a**, **28b**, **30a**, **30b**) probably form by a keto-enol tautomerisation and subsequent attack of an iodine molecule on the double bond of the corresponding enol **G**. This unusual kind of structural rearrangement involving the contraction from a ten- to a nine-membered ring has been only reported in two previous examples.[38]

In the aforementioned reaction pathway, the alkoxy group could play several roles.[37,38c] It may facilitate the radical addition to the ketone on C-5, by activating the carbonyl group, and it can assist in the ring opening of the intermediate cyclopropyloxy free radical by stabilizing the resulting free radical in **E** (Scheme 5). Apart from the possible electronic effects, some kind of Thorpe–Ingold[39] effect could be responsible for the "facilitation" of the cyclization process to afford the cyclopropyloxy radical. According to studies by Beckwith and Hay,[38d] the cycloaddition of free radicals to a carbonyl group are much slower than the ring openings of the resultant cyclic alkoxy radicals. Thus, the driving force to facilitate the approach of the carbonyl carbon atom and the carbon atom bearing the free radical could be the presence of sterically demanding substituents α to the carbonyl group. A captodative effect,[40] involving steric and electronic contributions,[39,40] could explain the different behaviour of substrate **27** and **25** or **27** and **26** upon exposure to LTA/I_2. These aspects are being studied now in our laboratory, by introducing bulkier substituents different from OEt or OMe α to the ketone in precursors **25** or **26**.

To confirm some aspects of the proposed mechanism, the ketone group at C-4 in **25** was reduced in order to avoid an intramolecular free-radical addition to that position. The ketone group in **25** was reduced by $NaBH_4$ in high yield and in a diastereospecific manner (Scheme 6) and the resulting alcohol **35** was quantitatively acetylated to obtain compound **36**. The obtained acetylated product was treated with LTA/I_2 (molar ratio of 1:1:1 at room temperature for 3 h) to obtain cyclodecane **37** in 75% yield and complete stereoselectivity regarding the insertion of an iodine atom into the newly formed stereocenter at C-7 (no other stereoisomers of **37** were detected). The stereoselectivity in the formation of **37** could be explained by the high steric demand of the iodine atom, which in the epimer of **37** would strongly interact with both the hydrogen atoms on C-9 and C-10 and the ethoxy group on C-6. The stereochemistry of **37** has been confirmed by X-ray diffraction analysis.



Scheme 6. Reduction, acetylation and β-fragmentation of **25** to generate **37**.

It is also important to remark that when working under mild reaction conditions (room temp. and no irradiation with artificial light), the formation of iodinated products was preferred to the formation of the acetoxylated ones irrespective of the molar ratio of substrate/LTA/I_2 (1:1:1 or 1:3:1). Thus, when substrates **25** and **26** were allowed to react under these mild conditions aldehyde **32** was isolated as the major product due to the reaction mechanism according to the proposed path (d) instead of path (c) (see Scheme 5). The aldehyde formation could be understood by considering the formation of an unstable iodinated intermediate **F** (instead of the stable acetals **29a**,**b** or **31a**,**b**) which could be easily hydrolyzed,[41] during workup, to afford the formylated compound.

The possible reason for the preference of path (d) over the path (c) could be the fact that the low concentration of acetoxy free radicals present in the reaction medium due to $Pb(OAc)_4$ does not decompose into $Pb(OAc)_2$ and $AcO^{\cdot}$ under mild reaction conditions. For this same reason, when **27** was treated with LTA/I_2 under mild conditions (see Table 3), only the iodinated products **33a**,**b** were isolated.

Moreover, when compound **36** was submitted to the aforementioned reaction conditions, the iodinated product **37** was formed as a unique product and no diacetoxy derivatives were detected in the crude reaction mixture. Compound **37** was physically and spectroscopically characterized and its structure was confirmed by X-ray diffraction analysis on single crystals (Figure 4).

In order to evaluate a possible thermodynamic driving force for the different mechanism paths to take place, calculations were performed to estimate the inner energy and formation enthalpy of key intermediates.[38d,42] The inner energy was calculated by using an MM2 program (the molecular mechanics algorithm was modified by the inclusion of adequate parameters for carbon-centred free radicals) and the formation enthalpy by the semi-empirical quantum chemistry package MOPAC, using an AM1 algorithm and UHF functions for the intermediate free radicals. The obtained data are expressed in kcal/mol and quoted in Table 5. These data, with the limitations established by the accuracy of the calculation methods, support the proposed mechanism in the following aspects:

(1) According to the calculated formation enthalpy data, the stability of intermediates **A**–**F** increases within the series R = H < R = OMe < R = OEt. So, the size and type of substituent R certainly influences the stability of these intermediates.

(2) The inner energy of cyclopropyloxy radical **D**, as expected, is much higher than that of the other intermediates due to the annular strain of the cyclopropane subunit (see Entries 7–9 in Table 5). On the other hand, the transformation **C** → **D** affords a positive reaction enthalpy (ΔH_r), decreasing within the series R = OEt < R = OMe < R = H (see Entries 10–12, Table 5). However, in the last case (R = H) the formation of intermediate **D** is more unfavourable than in the other two cases. This could be one of the reasons that justifies in some way the preference of path (a) for substrates with R = OEt, OMe.

(3) The transformation **A** → **B** is thermodynamically favoured in all cases but without differences in ΔH_r among substrates (see Entries 4–6, Table 5). However, the transformation **B** → **C** requires the absorption of energy to generate the tertiary free radical **C** and the process takes place without appreciable differences amid the three types of substrates due to the fact that the C-8 position in **C** is not involved in the β-scission reaction.

(4) In the transformation **D** → **E** (second β-scission), the variation of enthalpy (ΔH_r) is more favourable in the case of R = OEt or R = OMe than it is for R = H. This could be due to the virtual formation of a highly unstable primary free radical **E** in the case of R = H. This may be the other reason to justify the preference of substrate **27** (R = H) for the reaction path (b) (Scheme 5).

(5) The preference of path (c) over path (d) is consistent with the higher formation enthalpy of products **29a**,**b**/**31a**,**b** compared with that of **F** or **32**. Moreover, there is a great difference between the reaction enthalpies (ΔH_r) of transformations **E** → **F** (Entries 16–18, Table 5) vs. the enthalpy of process **E** → **29** or **E** → **31** (Entries 19–22, Table 5). The difference in stability between **F** and **29a**,**b** or **31a**,**b** is corroborated also by the experimental or empirical observation. Thus, **F** could be detected but could not be isolated because it was readily transformed into **32** under the reac-

Table 5. Inner energy and formation enthalpies calculated for the intermediates of the proposed reaction mechanism.

Entry	Intermediate	Inner energy (MM2) [kcal/mol]	Formation enthalpy {MOPAC (AM1)}[a] [kcal/mol]	Reaction enthalpies $\Delta H_r = \Delta H_f^2 - \Delta H_f^1$ [kcal/mol] Transformations									
				A → B	**B → C**	**C → D**	**D → E**	**E → F**	**F → 32**	**E → 29**	**E → 31**	**C → 33**	**C → 34**
1	**A** (R = OEt)	52.53	–131.56	–	–	–	–	–	–	–	–	–	–
2	**A** (R = OMe)	52.03	–126.15	–	–	–	–	–	–	–	–	–	–
3	**A** (R = H)	44.16	–91.05	–	–	–	–	–	–	–	–	–	–
4	**B** (R = OEt)	46.31	–179.60	–48.04	–	–	–	–	–	–	–	–	–
5	**B** (R = OMe)	45.81	–174.02	–47.87	–	–	–	–	–	–	–	–	–
6	**B** (R = H)	38.01	–138.76	–47.71	–	–	–	–	–	–	–	–	–
7	**C** (R = OEt)	33.13	–148.93	–	30.67	–	–	–	–	–	–	–	–
8	**C** (R = OMe)	32.65	–143.36	–	30.66	–	–	–	–	–	–	–	–
9	**C** (R = H)	28.16	–108.29	–	30.47	–	–	–	–	–	–	–	–
10	**D** (R = OEt)	178.42	–132.50	–	–	16.43	–	–	–	–	–	–	–
11	**D** (R = OMe)	177.98	–126.84	–	–	16.52	–	–	–	–	–	–	–
12	**D** (R = H)	174.04	–89.96	–	–	18.33	–	–	–	–	–	–	–
13	**E** (R = OEt)	43.88	–144.81	–	–	–	–12.31	–	–	–	–	–	–
14	**E** (R = OMe)	44.65	–138.68	–	–	–	–11.84	–	–	–	–	–	–
15	**E** (R = H)	31.94	–95.41	–	–	–	–5.45	–	–	–	–	–	–
16	**F** (R = OEt)	53.25	–144.04	–	–	–	–	0.77	–	–	–	–	–
17	**F** (R = OMe)	47.69	–134.96	–	–	–	–	3.72	–	–	–	–	–
18	**F** (R = H)	35.64	–112.46	–	–	–	–	–17.05	–	–	–	–	–
19	(1′*R*)-**29a** (R = OEt)	68.61	–230.53	–	–	–	–	–	–	–85.72	–	–	–
20	(1′*S*)-**29b** (R = OEt)	70.33	–230.26	–	–	–	–	–	–	–85.45	–	–	–
21	(1′*R*)-**31a** (R = OMe)	68.31	–224.74	–	–	–	–	–	–	–	–86.06	–	–
22	(1′*S*)-**31b** (R = OMe)	69.57	–224.69	–	–	–	–	–	–	–	–86.01	–	–
23	**32**	43.75	–150.25	–	–	–	–	–	–6.21	–	–	–	–
24	(7*S*)-**33a** (R = H)	31.44	–112.19	–	–	–	–	–	–	–	–	–3.90	–
25	(7*S*)-**34a** (R = H)	36.47	–211.57	–	–	–	–	–	–	–	–	–	–103.28
26	(7*R*)-**33b** (R = H)	31.40	–107.63	–	–	–	–	–	–	–	–	0.66	–
27	(7*R*)-**34b** (R = H)	35.54	–210.23	–	–	–	–	–	–	–	–	–	–101.94

[a] In the case of free radicals a UHF function was used.

tion conditions, meanwhile **29** and **31** were quite stable compounds, which could be isolated, purified and characterized without any decomposition problems.

Conclusions

A versatile methodology based on the hypoiodite reaction has been developed to synthesize either 1,7-epoxycyclononanes or 1,8-epoxycyclodecanes with a high level of functionalisation, starting from the same tricyclic precursor, which is available, in good yield and in enantiomerically pure form, by a procedure also developed by the authors based on three key steps: a [4+3] cycloaddition followed by a Nicholas reaction and a stereoconvergent aldol cyclization. A systematic study of the reaction conditions has been performed and the main factors controlling the reaction outcomes have been unveiled. Also, a possible mechanism to explain the ring contraction has been proposed and corroborated by the implication of a free-radical addition to the ketone on C-5 of intermediate **C**, by reducing the corresponding carbonyl group in the substrate **25** and protecting the resultant alcohol. Thus, no rearrangements and ring contractions were observed for substrate **36**, but only the β-fragmentation product **37** was obtained in 75% yield.

Experimental Section

General Experimental Procedures: Unless otherwise noted, all reactions were conducted under dry nitrogen or argon in oven-dried glassware. All solvents were purified using standard techniques before use; diethyl ether, tetrahydrofuran, hexane and pentane were distilled under nitrogen from sodium/benzophenone. Acetonitrile was distilled under nitrogen from CaH_2. Infrared spectra were recorded with an FT-IR Nicolet 510 spectrophotometer as thin films between NaCl plates. NMR spectra were recorded in $CDCl_3$ with Varian spectrometers at 200 MHz (Gemini-200), 400 MHz (Mercury-400) or 500 MHz (Uunity-500) for ^1H NMR, and at 50 MHz or 100 MHz for ^{13}C NMR spectroscopy. For ^1H NMR tetramethylsilane was used as an internal standard. ^{13}C NMR spectra were referenced to the δ = 77.0 ppm resonance of chloroform. Mass spectra were measured with a Hewlett–Packard 5890 mass spectrometer using chemical ionization. GC analyses were performed with an HP-8790 gas chromatograph equipped with a Hewlett–Packard crosslinked 5% MePhe-Silicone capillary column (L = 25 m, D = 0.2 mm, thickness = 2.5 μm) using helium as a carrier gas and an FID detector (T = 250 °C, P_{H_2} = 4.2 psi, P_{air} = 2.1 psi). Elemental analyses were obtained with a Fisons elemental analyzer, model Na-1500. The samples were previously pyrolised at 1000 °C under oxygen, and the content of carbon and hydrogen was determined by the evaluation of the combustion gases by gas chromatography using an FID detector.

X-ray Diffraction Analysis: Suitable crystals (0.1 × 0.1 × 0.2 mm) from compounds **25**, **28a**, **32** and **37** were selected and mounted on a MAR345 apparatus with an image plate detector. Unit-cell parameters were determined from automatic centring of reflections and refined by the least-squares method. Intensities were collected with graphite-monochromatised Mo-K_α radiation. Lorentz-polarization and absorption corrections were made. The structures were solved by direct methods and refined by the full-matrix least-squares method using the SHELXS-97 computer program,[43] on the basis of the non-equivalent reflections by symmetry (very negative intensities were not assumed). The function minimized was: $\Sigma w[(F_o)^2 - (F_c)^2]^2$, where $w = [\sigma^2(I) + (0.0745P)^2 + 0.4463P)^{-1}$, and $P = [(F_o)^2 + 2(F_c)^2]/3$; f, f' and f'' were taken from the International Tables of X-ray Crystallography.[44] All the H atom positions were computed and refined, using a riding model, with isotropic temperature factor equal to 1.2 times the equivalent temperature factor of the atoms to which they are linked. The final R (on F) factors and goodness of fit are shown in Table 5. The number of refined parameters was 127; max. shift/esd = 0.00; mean shift/esd = 0.00. The refinement of F^2 was performed against all reflections. The weighted R factor, wR, and goodness of fit, S, are based on F^2; conventional R factors R are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R factors for observed reflections and is not relevant to the choice of reflections for refinement. R factors based on F^2 are statistically about twice as large as those based on F, and R factors based on all data are even larger. All esds (except the esd in the dihedral angle between two least-squares planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving least-squares planes. The main X-ray data are quoted in Table 6. Selected bond lengths and bond angles for compounds **25**, **28a**, **32** and **37** are quoted in Tables S1 and S2, respectively, in the Supporting Information (the numbering is in agreement with the IUPAC nomenclature). CCDC-622959, -622960, -622961 and -622962 for compounds **25**, **28a**, **32** and **37**, respectively, contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Synthetic Methodology to Prepare the Oxatricyclic Compounds: The methodology to synthesize compounds **25**, **26** and **27** is exemplified for the preparation of **27**. The intermediates and final products described herein are all new compounds, characterized by the first time. The understanding of proton and carbon assignments in the NMR spectra can be facilitated by looking at the numbering of atoms in Figure 4, Table 4 and Scheme 4.

Synthesis of Hexacarbonyl{μ-[η⁴-(1-hydroxyprop-3-yne)]}dicobalt(Co–Co) (15): In a 100 mL round-bottomed flask, fitted with magnetic stirring bar, nitrogen inlet and equalizing-pressure addition funnel, hexacarbonyldicobalt (0.73 g, 2.142 mmol) was dissolved in anhydrous hexane (15 mL). Propargyl alcohol (**14**, 0.1 g, 1.725 mmol), dissolved in anhydrous hexane (5 mL), was then added dropwise. The reaction mixture was stirred at room temperature for 3 h (monitored by TLC). Afterwards, the reaction mixture was percolated through a short pad of activated neutral alumina and eluted with anhydrous diethyl ether, in order to remove the possible excess of hexacarbonyldicobalt. The organic solutions were combined and concentrated to dryness in a rotary evaporator (without heating!). Thus, a dark red oil of product **15** was obtained (630 mg, conversion 100%, yield 100%). IR (film): $\tilde{\nu}$ = 3395 (O–H, st), 2909, 2855 (Csp^3–H, st), 2099, 2016 (C≡C, st), 1341, 1034 (C–O, st) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 4.81 (dd, J_1 = 0.6, J_2 = 6.2 Hz, 2 H, 1-H), 6.07 (s, 1 H, 3-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 63.2 (C-1), 71.3 (C-3), 199.4, 201.5 (C-2) ppm. MS (DIP-CI-NH_3, 70 eV, 150 °C): m/z (%) = 314 (1) [M – CO], 230 (13) [M – 4 CO]. TLC (SiO_2; hexane/diethyl ether, 3:7; developed with anisaldehyde): R_f = 0.48. $C_9H_4Co_2O_7$ (341.99): calcd. C 31.6, H 1.18; found C 31.58, H 1.21.

Table 6. Crystal data refinement for **25**, **28a**, **32** and **37**.

	25	**28a**	**32**	**37**
Temperature	150(2) K	150(2) K	150(2) K	293(2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	orthorhombic	orthorhombic	triclinic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P\bar{1}$	$P2_12_12_1$
Unit cell dimensions	a = 6.30400(10) Å, α = 90°	a = 11.9860(2) Å, α = 90°	a = 6.47900(10) Å, α = 13.3290(10)°	a = 9.070(4) Å, α = 90°
	b = 13.5660(2) Å, β = 90°	b = 12.3380(2) Å, β = 90°	b = 9.0520(2) Å, β = 104.4530(10)°	b = 15.521(6) Å, β = 90°
	c = 15.8370(3) Å, γ = 90°	c = 12.3940(2) Å, γ = 90°	c = 10.4950(2) Å, γ = 91.3010(10)°	c = 26.457(6) Å, γ = 90°
Volume	1354.38(4) Å^3	1832.87(5) Å^3	542.165(18) Å^3	3724(2) Å^3
Z	4	4	2	8
Calculated density	1.247 Mg/m^3	1.588 Mg/m^3	1.374 Mg/m^3	1.513 Mg/m^3
Absorption coefficient	0.090 mm^{-1}	1.773 mm^{-1}	0.103 mm^{-1}	1.738 mm^{-1}
F(000)	552	880	240	1712
Crystal size	0.30×0.15×0.10 mm	0.25×0.15×0.10 mm	0.50×0.25×0.10 mm	0.2×0.1×0.1 mm
θ range for data collection	3.48–27.49°	3.78–30.99°	5.56–29.17°	2.71 to 30.00°
Limiting indices	$-8 \le h \le 8$	$-16 \le h \le 17$	$-8 \le h \le 8$	$0 \le h \le 11$
	$-17 \le k \le 17$	$-17 \le k \le 17$	$-12 \le k \le 12$	$0 \le k \le 20$
	$-20 \le l \le 20$	$-17 \le l \le 17$	$-14 \le l \le 14$	$0 \le l \le 36$
Reflections collected	22345	19536	15755	27047
Independent reflections	3094 [R (int) = 0.0808]	5759 [R (int) = 0.0444]	2882 [R (int) = 0.0319]	27047 [R (int) = 0.0584]
Completeness to θ	27.49° (99.7%)	30.99° (99.3%)	29.17° (98.6%)	30.00° (82.7%)
Max./min. transmission	0.9911/0.9735	0.8426/0.6656	0.9898/0.9505	–
Refinement method	full-matrix least squares on F^2	full-matrix least squares on F^2	full-matrix least squares on F^2	full-matrix least squares on F^2
Data/restraints/parameters	3094/0/167	5759/0/208	2882/0/147	4491/0/208
Goodness-of-fit on F^2	1.061	1.025	1.051	1.066
Final R indices [$I>2\sigma(I)$]	R_1 = 0.0497, wR_2 = 0.1125	R_1 = 0.0296, wR_2 = 0.0608	R_1 = 0.0357, wR_2 = 0.0940	R_1 = 0.0632, wR_2 = 0.1774
R indices (all data)	R_1 = 0.0634, wR_2 = 0.1175	R_1 = 0.0338, wR_2 = 0.0626	R_1 = 0.0404, wR_2 = 0.0975	R_1 = 0.0780, wR_2 = 0.1898
Absolute structure parameter	–0.4(12)	–0.009(14)	–	–
Largest diff. peak/hole	0.545/–0.535 e Å^{-3}	0.570/–1.026 e Å^{-3}	0.0305/–0.174 e Å^{-3}	0.618/–0.691 e Å^{-3}

Synthesis of Hexacarbonyl(μ-{η^4-[2,4-dimethyl-2-(prop-2-yn-1-yl)-8-oxabicyclo[3.2.1]octan-3-one]})dicobalt(Co–Co) (18): In a 50 mL flask fitted with magnetic stirring bar, argon inlet and septum, compound **15** (150 mg, 0.440 mmol) was dissolved in anhydrous dichloromethane (2 mL). Then, 2,4-dimethyl-3-[(trimethylsilyl)-oxy]-8-oxabicyclo[3.2.1]oct-2-ene (**6**, 90 mg, 0.4 mmol), dissolved in anhydrous dichloromethane (2 mL), was added by cannula. The mixture was cooled to 0 °C, and $BF_3{\cdot}OEt_2$ (300 μL, 2.0 mmol) was added all at once. The reaction mixture was maintained at 0 °C for 5 min and then allowed to warm to room temperature. After 2 h (monitored by TLC), the reaction mixture was quenched at 0 °C by the addition of triethylamine (400 μL, 2.5 mmol) and washed with iced water. The organic solution was dried with anhydrous $MgSO_4$, filtered and then percolated through a short pad of activated neutral alumina, eluting with dichloromethane. The organic solution was concentrated to dryness in a rotary evaporator (without heating!), giving **18** as a dark red oil (190 mg, conversion 100%, yield 98%). IR (film): $\tilde{\nu}$ = 2983 (Csp^3–H, st), 2093, 2053, 2024 (C≡C st),1711 (C=O, st), 1381, 1157, 1028, 1047 (C–O, st) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 0.94 (d, J = 7 Hz, 3 H, 10-H), 1.09 (s, 3 H, 9-H), 1.30–1.80 (m, 4 H, 6-H and 7-H), 2.93 (m, 1 H, 4-H), 3.33 (d, J = 14 Hz, 1 H, 1′-H), 4.00 (d, J = 14 Hz, 1 H, 1′-H), 4.25 (d, J = 7 Hz, 1 H, 1-H), 4.55 (dd, 1 H, 5-H), 5.59 (s, 1 H, 3′-H) ppm. TLC (SiO_2; hexane/diethyl ether, 8:2; developed with anisaldehyde): R_f = 0.44. $C_{18}H_{16}Co_2O_8$ (478.95): calcd. C 45.21, H 3.37; found C 45.25, H 3.41.

Preparation of 2,4-Dimethyl-2-(prop-2-yn-1-yl)-8-oxabicyclo[3.2.1]-octan-3-one (21): In a 25 mL round-bottomed flask, fitted with magnetic stirring bar, nitrogen inlet and septum, compound **18** (100 mg, 0.21 mmol) was dissolved in anhydrous acetone (5 mL). The solution was cooled to 0 °C, and triethylamine (55 μL, 0.42 mmol) was added all at once. At this temperature, CAN (575 mg, 1.05 mmol) was added (portionwise!) under vigorous stirring. The addition lasted 2 h, and the reaction mixture was maintained at 0 °C for an additional 1 h until complete demetallation (monitored by TLC) was observed by a change of colour from a dark red oil to an orange one. The reaction mixture was percolated through a three-layer short pad of Celite®, alumina and silica gel in this order, eluting with acetone. The solvent was evaporated in vacuo. The residue was dissolved in water/diethyl ether, decanted, and the aqueous solution was extracted with diethyl ether (4×20 mL). The organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated to dryness to obtain **21** (57 mg, conversion 100%, yield 95%). IR (film): $\tilde{\nu}$ = 3287, 2979, 2938 (Csp^3–H, st), 2118 (C≡C st), 1713 (C=O, st), 1472 (C–C, deform.), 1026, 1045, 931, 901 (C–O, st) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 0.94 (d, J = 6.8 Hz, 3 H, 10-H), 1.08 (s, 3 H, 9-H), 1.30–1.80 (m, 6-H and 7-H, 4-H), 2.03 (d, J = 2.8 Hz, 1 H, 3′-H), 2.69 (dd, J = 14, J = 2.8 Hz, 1 H, 1′-H), 2.94 (dq, 1 H, 4-H), 3.02 (dd, J = 14, J = 2.8 Hz, 1 H, 1′-H), 4.27 (d, J = 6.6 Hz, 1 H, 1-H), 4.46 (dd, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 9.9 (C-10), 16.7 (C-9), 24.3 (C_1′), 25.0 (C-7), 27.6 (C-6), 47.9 (C-4), 71.4 (C-3′), 81.0 (C-5), 82.4 (C-1) ppm. MS (DIP-CI-NH_3, 70 eV, 150 °C): m/z (%) = 190 (2) [M], 207 (22) [M + NH_3], 258 (100) [M + N_4H_{12}]. GC (T_i = 50 °C, t_i = 1 min, rate = 5 °C/min, T_f = 290 °C, t_f = 10 min): t_R = 15.35 min. TLC (SiO_2; hexane/diethyl ether, 8:2; developed with anisaldehyde): R_f = 0.46. $C_{12}H_{16}O_2$ (192.25): calcd. C 74.97, H 8.39; found C 75.01, H 8.35.

Synthesis of 2,4-Dimethyl-2-(2-oxopropyl)-8-oxabicyclo[3.2.1]octan-3-one (24): In a 100 mL three-necked round-bottomed flask, fitted with magnetic stirring bar and Dimroth condenser, compound **21** (250 mg, 1.30 mmol) was dissolved in ethanol/water (85:15, 30 mL). To this solution, Hg^{II} bis(p-toluenesulfonamidate) (0.914 g, 1.7 mmol) was added all at once, and the mixture was maintained at reflux for 24 h. Afterwards, the reaction mixture was cooled to room temperature, and ammonium sulfide (1.5 mL, 2.1 mmol) was added, and the precipitation of a black solid of mercury(II) sulfide was observed. The reaction mixture was percolated through a three-layer short pad of Celite®/alumina/silica gel (1:1:1), and the

resultant clear solution was concentrated to dryness. The residue was dissolved in diethyl ether and washed with aqueous NaOH (2 M, 2×25 mL). The alkaline aqueous phase was extracted with diethyl ether (2×10 mL), and all organic phases were combined, dried with anhydrous $MgSO_4$, filtered and concentrated to dryness. The resultant crude oil was purified by flash column chromatography on silica gel, eluting with mixtures of hexane and diethyl ether of increasing polarity, to isolate product **24** (244 mg, conversion 100%, yield 86%). IR (film): $\tilde{\nu}$ = 2975 (Csp^3–H, st) 1711 (C=O, st), 1472 (C–C, deform.), 1360, 1374, 1315, 1180, 1034, 1045 (C–O, st) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 0.94 (d, J = 6.6 Hz, 3 H, 10-H), 1.02 (s, 3 H, 9-H), 1.60–1.85 (m, 4 H, 6-H and 7-H), 2.13 (s, 1 H, 3′-H), 2.87 (d, J = 16.4 Hz, 2 H, 1′-H), 3.0 (dq, 1 H, 4-H), 3.23 (d, J = 16.4 Hz, 1 H, 1′-H), 4.32 (d, J = 6 Hz, 1 H, 1-H), 4.46 (dd, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 9.7 (C-10), 16.8 (C-9), 24.4 (C-6′), 24.5 (C-7), 31.5 (C-3′), 47.0 (C-1′), 50.4 (C-4), 50.3 (C-2), 81.7 (C-5), 83.0 (C-1), 210.5 (C-2′) ppm. MS (DIP-EI, 70 eV, 150 °C): m/z (%) = 210 (11) $[M]^+$, 195 (5) [M – CH_3], 180 (6) [M – 2 CH_3], 154 (14) [M – CH_2COCH_3], 124 (2) [M – $C_5H_{10}O$], 107 (100) [M – $C_5H_{11}O_2$]. GC (T_i = 100 °C, t_i = 1 min, rate = 10 °C/min, T_f = 250 °C, t_f = 10 min): t_R = 12.77 min. TLC (SiO_2; hexane/diethyl ether, 8:2; developed with anisaldehyde): R_f = 0.57. $C_{12}H_{18}O_3$ (210.27): calcd. C 68.54, H 8.63; found C 68.60, H 8.61.

Synthesis of 2,7-Dimethyl-6-hydroxy-11-oxatricyclo[6.2.1.0^{2,6}]undecan-4-one (27). (a) Preparation of Anhydrous KOH: In a 100 mL flask, commercial KOH (3 g), in lentils, was dissolved in absolute ethanol (10 mL). Afterwards, benzene (15 mL) was added, and the flask was connected to a Dean–Stark system. The azeotropic distillation was maintained in such a way that first the azeotrope benzene/ethanol/water (74.1:18.5:7.4) with a b.p. of 64.6 °C distilled and then the benzene/ethanol azeotrope (67.6:32.4) with a b.p. of 68.3 °C distilled. Finally, the solution was concentrated to dryness, and the resulting white solid was dried in vacuo for 6 h, ground and readily used. **(b) Aldol Cyclization:** In a 25 mL round-bottomed flask, fitted with magnetic stirring bar, argon inlet and septum, **24** (175 mg, 0.82 mmol) was placed. Freshly prepared anhydrous KOH (642 mg, 11.48 mmol), dissolved in absolute ethanol (10 mL), was then added all at once by cannula. The reaction mixture was maintained at room temperature for 18 h (monitored by TLC). The solvent was removed in a rotary evaporator, and the residue was dissolved in water. The aqueous solution was neutralized with 2 M HCl. The organic solution was extracted with diethyl ether (5×20 mL), the organic phases were combined, dried with anhydrous $MgSO_4$, filtered and concentrated to dryness to obtain a white solid, which was purified by flash column chromatography on silica gel, eluting with mixtures of hexane and diethyl ether of increasing polarity. Pure product **27** was isolated (134 mg, conversion 95%, yield 78%). IR (film): $\tilde{\nu}$ = 3442 (O–H, st), 2952 (Csp^3–H, st) 1742 (C=O, st) 1256, 1167, 1107, 1045 (C–O, st) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 0.92 (d, J = 6.8 Hz, 3 H, 13-H), 1.01 (s, 3 H, 12-H), 1.60–2.00 (m, 4 H, 9-H and 10-H), 1.90 (dq, J = 4 Hz, 1 H, 7-H), 2.02 (d, J = 19 Hz, 1 H, 5-H), 2.30 (d, J = 17.8 Hz, 1 H, 3-H), 2.37 (dd, J = 17.8 Hz, 1 H, 3-H), 3.13 (d, J = 19 Hz, 1 H, 5-H), 3.93 (d, J = 6 Hz, 1 H, 1-H), 4.13 (dd, J = 3, J = 6.8 Hz, 1 H, 8-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 9.9 (C-13), 18.9 (C-12), 23.8 (C-10), 24.6 (C-9), 39.8 (C-2), 45.8 (C-7), 50.4 (C-3), 51.4 (C-5), 76.3 (C-8), 79.0 (C-1) 209.0 (C-4) ppm. MS (DIP-EI, 70 eV, 150 °C): m/z (%) = 210 (16) $[M]^+$, 155 (12) [M – CH_2COCH_3], 139 (26) [M – $C_3H_5O_2$], 124 (37) [M – $C_4H_8O_2$], 109 (75) [M – $C_5H_{11}O_2$], 93 (100) [M – $C_6H_{14}O_2$]. GC (T_i = 100 °C, t_i = 1 min, rate = 10 °C/min, T_f = 250 °C, t_f = 10 min): t_R = 19.49 min. TLC (SiO_2; hexane/diethyl ether, 7:3; developed with anisaldehyde): R_f = 0.24. $C_{12}H_{18}O_3$ (210.27): calcd. C 68.54, H 8.63; found C 68.49, H 8.67.

General Procedure for the Synthesis of 28a, 28b, 29a and 29b by β-Fragmentation Reactions: Into a 100 mL flask, previously heated under vacuum and purged with argon, compound **25** (159 mg, 0.62 mmol) was added. Subsequently, LTA (824 mg, 1.86 mmol) and I_2 (157 mg, 0.62 mmol) were added all at once under an argon flow. The resulting solid mixture was dissolved in anhydrous benzene (2 mL) and irradiated with two 100 W lamps for 2 h. The reaction temperature was stabilized at 45–50 °C, and the reaction was monitored by TLC. When the reaction was complete (100% conversion of **1**), the mixture was allowed to cool to room temperature, and then the reaction mixture was percolated through a short column of Celite®, eluting with diethyl ether. The organic solution was then concentrated in a rotary evaporator to a volume of 20 mL and subsequently extracted with aq. $NaHCO_3$ (1.2 M, 3×20 mL), aq. $Na_2S_2O_3$ (5% w/w, 4×25 mL) and finally with distilled water (25 mL). The organic phase was dried with anhydrous $MgSO_4$, filtered and concentrated to dryness to afford 245 mg of product. The product was submitted to flash column chromatography (SiO_2), eluting with mixtures of hexane (H) and diethyl ether (E) of increasing polarity to isolate 114 mg of **28a** (with H/E, 60:40), 43 mg of **28b** (with H/E 30: 70), 53.6 mg of **29a** (with H/E, 50:50) and 25.8 mg of **29b** (with H/E, 20:80).

(*R*)-(Ethoxy){(1*R*,2*S*,4*R*,6*R*,7*S*)-4-iodo-2,6-dimethyl-3,5-dioxo-10-oxabicyclo[5.2.1]dec-2-yl}methyl Acetate (28a): IR (film): $\tilde{\nu}$ = 3459 (O–H, st), 2981, 2938 (Csp^3–H, st), 1733 (C=O, st), 1701 (C=O), 1231 (C–O, st), 1105, 1061, 1028 (C–O, st) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.01 (d, J = 6.6 Hz, 3 H, 11′′-H), 1.08 (s, 3 H, 12′′-H), 1.26 (t, J = 7.2 Hz, 3 H, 2′′′-H), 1.75–2.14 (m, 4 H, 8′′-H and 9′′-H), 2.11 (s, 3 H, 2-H), 3.34 (dq, J = 6.6, J = 6.5 Hz, 1 H, 6′′-H), 3.84 (dq, J = 10.25, J = 7 Hz, 1 H, 1′′′-H), 3.89 (dq, J = 9.8, J = 7 Hz, 1 H, 1′′′-H), 4.31 (dd, J = 8, J = 7.6 Hz, 1 H, 1′′-H), 4.45–4.54 (m, 1 H, 7′′-H), 5.69 (s, 1 H, 1′-H), 6.73 (s, 1 H, 4′′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 11.9 (C-12′′), 12.1 (C-11′′), 15.09 (C-2′′′), 21.7 (C-2), 25.6 and 26.6 (C-8′′ and C-9′′), 33.7 (C-1′), 53.3 (C-6′′), 66.9 (C-1′′′), 82.3 and 83.6 (C-1′′ and C-7′′), 96.1 (C-4′′), 171.0 (C-1), 197.0 (C-3′′), 201.4 (C-5′′) ppm. MS (DIP-CI-NH_3, 70 eV, 150 °C): m/z (%) = 456 (10) $[M + NH_4]^+$, 438 (1) [M], 379 (22) [M – $C_2O_2H_3$], 311 (9) [M – I], 207 (100) [M – I – $C_2O_2H_3$ – C_2H_5]. $C_{16}H_{23}IO_6$ (438.25): calcd. C 43.85, H, 5.29; found 43.91, H 5.32.

(*S*)-(Ethoxy){(1*R*,2*S*,4*R*,6*R*,7*S*)-4-iodo-2,6-dimethyl-3,5-dioxo-10-oxabicyclo[5.2.1]dec-2-yl}methyl Acetate (28b): IR (film): $\tilde{\nu}$ = 2981, 2935 (Csp^3–H, st), 1733 (C=O, st), 1701 (C=O), 1234 (C–O, st), 1106, 1062, 1009 (C–O, st) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.01 (d, J = 6.8 Hz, 3 H, 11′′-H), 1.08 (s, 3 H, 12′′-H), 1.23 (t, J = 7.0 Hz, 3 H, 2′′′-H), 1.8–2 (m, 4 H, 8′′-H and 9′′-H), 2.18 (s, 3 H, 2-H), 3.35 (dq, J = 6.2, J = 6.4 Hz, 1 H, 6′′-H), 3.63 (dq, J = 9.4, J = 7 Hz, 1 H, 1′′′-H), 3.7 (dq, J = 9.2, J = 7.0 Hz, 1 H, 1′′′-H), 4.03 (dd, J = 8.0, J = 8.0 Hz, 1 H, 1′′-H), 4.4–4.5 (m, 1 H, 7′′-H), 5.79 (s, 1 H, 1′-H), 6.76 (s, 1 H, 4′′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.0 (C-12′′), 12.4 (C-11′′), 15.1 (C-2′′′), 21.3 (C-2), 25.8 and 26.8 (C-8′′ and C-9′′), 32.6 (C-1′′), 53.2 (C-6′′), 63.8 (C-2′′), 66.2 (C-1′′′), 82.1 and 83.9 (C-1′′ and C-7′′), 96.1 (C-4′′), 170.9 (C-1), 196.7 (C-3′′), 201.8 (C-5′′) ppm. MS (DIP-CI-NH_3, 70 eV, 150 °C): m/z (%) = 456 (10) $[M + NH_4]^+$, 438 (1) [M], 379 (22) [M – $C_2O_2H_3$], 311 (9) [M – I], 207 (100) [M – I – $C_2O_2H_3$ – C_2H_5]. $C_{16}H_{23}IO_6$ (438.25): calcd. C 43.85, H, 5.29; found C 43.95, H, 5.40.

(*R*)-{(1*R*,2*S*,6*R*,7*S*)-2,6-Dimethyl-3,5-dioxo-10-oxabicyclo[5.2.1]-dec-2-yl}(ethoxy)methyl Acetate (29a): IR (film): $\tilde{\nu}$ = 3449 (O–H,

st), 2978, 2936 (Csp^3–H, st), 1725 (C=O, st), 1695 (C=O), 1233 (C–O, st), 1107, 1062, 1010 (C–O, st) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.94 (d, J = 6.8 Hz, 3 H, 11′′-H), 1.02 (s, 3 H, 12′′-H), 1.27 (t, J = 7.2 Hz, 3 H, 2′′′-H), 1.75–2.0 (m, 4 H, 8′′-H and 9′′-H), 2.01 (s, 3 H, 2-H), 2.98 (d, J = 8.4 Hz, 1 H, 4′′-H), 3.30 (dq, J = 6.4, J = 6.4 Hz, 1 H, 6′′-H), 3.79 (dq, J = 9.6, J = 7 Hz, 1 H, 1′′′-H), 3.87 (dq, J = 9.4, J = 7.0 Hz, 1 H, 1′′′-H), 4.29 (dd, J = 8.0, J = 8.0 Hz, 1 H, 1′′-H), 4.4–4.5 (m, 1 H, 7′′-H), 4.57 (d, J = 8.4 Hz, 1 H, 4′′-H) 6.75 (s, 1 H, 1′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 11.6 (C-12′′), 11.6 (C-11′′), 15.3 (C-2′′′), 21.2 (C-2), 25.9 and 26.9 (C-8′′ and C-9′′), 54.2 (C-6′′), 57.9 (C-4′′), 63.1 (C-2′′), 66.9 (C-1′′′), 82.9 and 84.1 (C-1′′ and C-7′′), 97.6 (C-1′), 199.8 (C-3′′), 203.0 (C-5′′) ppm. MS (DIP-CI-NH_3, 70 eV, 150 °C): m/z (%) = 330 (11) $[M + NH_4]^+$, 270 (47) [M – C_2H_2O], 253 (100) [M – $C_2O_2H_3$], 222 (30) [M – $C_2O_2H_3$ – C_2H_5]. $C_{16}H_{24}O_6$ (312.36): calcd. C 61.52, H 7.74; found C 61.35, H 7.85.

(*S*)-{(1*R*,2*S*,6*R*,7*S*)-2,6-Dimethyl-3,5-dioxo-10-oxabicyclo[5.2.1]dec-2-yl}(ethoxy)methyl Acetate (29b): IR (film): $\tilde{\nu}$ = 3391 (O–H, st), 2979, 2937 (Csp^3–H, st), 1748, 1725 (C=O, st), 1694 (C=O), 1239 (C–O, st), 1106, 1062, 1001 (C–O, st) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.93 (d, J = 6.8 Hz, 3 H, 11′′-H), 1.03 (s, 3 H, 12′′-H), 1.12 (t, J = 7.0 Hz, 3 H, 2′′′-H), 1.5–2.0 (m, 4 H, 8′′-H and 9′′-H), 2.18 (s, 3 H, 2-H), 3.18 (d, J = 8.0 Hz, 1 H, 4′′-H), 3.33 (dq, J = 6.4, J = 6.4 Hz, 1 H, 6′′-H), 3.56 (dq, J = 9.6, J = 7 Hz, 1 H, 1′′′-H), 3.72 (dq, J = 9.6, J = 7.0 Hz, 1 H, 1′′′-H), 3.99 (dd, J = 6.8, J = 6.8 Hz, 1 H, 1′′-H), 4.34–4.42 (m, 1 H, 7′′-H), 4.54 (d, J = 8.0 Hz, 1 H, 4′′-H) 6.83 (s, 1 H, 1′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 11.4 (C-12′′), 11.5 (C-11′′), 14.9 (C-2′′′), 21.2 (C-2), 25.8 and 26.6 (C-8′′ and C-9′′), 53.9 (C-6′′), 57.4 (C-4′′), 65.8 (C-1′′′), 82.4 and 83.7 (C-1′′ and C-7′′), 96.3 (C-1′) ppm. MS (DIP-CI-NH_3, 70 eV, 150 °C): m/z (%) = 330 (12) $[M + NH_4]^+$, 313 (3) [M + 1], 270 (40) [M – C_2H_2O], 253 (100) [M – $C_2O_2H_3$]. $C_{16}H_{24}O_6$ (312.36): calcd. C 61.52, H 7.74; found C 61.64, H 7.69.

Synthesis of β-Fragmentation Products 30a, 30b, 31a and 31b: Into a 100 mL flask, previously heated under vacuum and purged with argon, compound **26** (141 mg, 0.59 mmol) was placed. Subsequently, LTA (781 mg, 1.76 mmol) and I_2 (149 mg, 0.59 mmol) were added all at once under argon. The resulting solid mixture was dissolved in anhydrous benzene (2 mL) and irradiated with two 100 W lamps for 2 h. The reaction temperature was kept at 45–50 °C, and the reaction was monitored by TLC. Once the reaction was complete, the mixture was allowed to cool to room temperature, and then it was percolated through a short pad of Celite®, eluting with diethyl ether. The organic solution was then concentrated to a volume of 20 mL and subsequently washed with aq. $NaHCO_3$ (1.2 M, 3 × 20 mL), aq. $Na_2S_2O_3$ (5% w/w, 4 × 25 mL) and distilled water (25 mL). The organic fraction was dried with $MgSO_4$, filtered and concentrated to dryness to afford 227 mg of an oily product. The product was submitted to flash column chromatography on silica gel to obtain 82.5 mg of **30a** (with H/E, 50:50), 57.5 mg of **30b** (with H/E, 30:70), 40.4 mg of **31a** (with H/E, 40:60) and 36.9 mg of **31b** (with H/E, 20:80).

(*R*)-{(1*R*,2*S*,4*R*,6*R*,7*S*)-4-Iodo-2,6-dimethyl-3,5-dioxo-10-oxabicyclo[5.2.1]dec-2-yl}(methoxy)methyl Acetate (30a): IR (film): $\tilde{\nu}$ = 3399 (O–H, st), 2978, 2942 (Csp^3–H, st), 1741 (C=O, st), 1703 (C=O), 1233 (C–O, st), 1109, 1060, 1019 (C–O, st) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.00 (d, J = 6.8 Hz, 3 H, 11′′-H), 1.06 (s, 3 H, 12′′-H), 1.7–2 (m, 4 H, 8′′-H and 9′′-H), 2.12 (s, 3 H, 2-H), 3.33 (dq, J = 6.2, J = 6.4 Hz, 1 H, 6′′-H), 3.59 (s, 3 H, 1′′′-H), 4.30 (dd, J = 8, J = 8 Hz, 1 H, 1′′-H), 4.46–4.52 (m, 1 H, 7′′-H), 5.69 (s, 1 H, 1′-H), 6.64 (s, 1 H, 4′′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.1 (C-12′′), 12.3 (C-11′′), 21.8 (C-2), 25.8 and 26.8 (C-8′′ and C-9′′), 33.9 (C-1′), 53.4 (C-6′′), 58.9 (C-1′′′), 63.9 (C-2′′), 82.6 and 83.9 (C-1′′ and C-7′′), 97.7 (C-4′′), 171.3 (C-1), 197.2 (C-3′′), 201.7 (C-5′′) ppm. MS (DIP-CI-NH_3, 70 eV, 150 °C): m/z (%) = 442 (100) $[M + NH_4]^+$, 365 (72.5) [M – AcO], 297 (8) [M – I]. $C_{15}H_{21}IO_6$ (424.23): calcd. C 42.47, H 4.99; found C 42.55, H 5.07.

(*S*)-{(1*R*,2*S*,4*R*,6*R*,7*S*)-4-Iodo-2,6-dimethyl-3,5-dioxo-10-oxabicyclo[5.2.1]dec-2-yl}(methoxy)methyl Acetate (30b): IR (film): $\tilde{\nu}$ = 3419 (O–H, st), 2939 (Csp^3–H, st), 1731 (C=O, st), 1699 (C=O), 1236 (C–O, st), 1107, 1061, 1007 (C–O, st) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.97 (d, J = 6.8 Hz, 3 H, 11′′-H), 1.06 (s, 3 H, 12′′-H), 1.8–2 (m, 4 H, 8′′-H and 9′′-H), 2.2 (s, 3 H, 2-H), 3.35 (dq, J = 6.4, J = 6.4 Hz, 1 H, 6′′-H), 3.44 (s, 3 H, 1′′′-H), 4.04 (dd, J = 8.0, J = 8.0 Hz, 1 H, 1′′-H), 4.40–4.60 (m, 1 H, 7′′-H), 5.79 (s, 1 H, 1′-H), 6.65 (s, 1 H, 4′′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.0 (C-12′′), 12.4 (C-11′′), 21.2 (C-2), 25.9 and 26.8 (C-8′′ and C-9′′), 32.2 (C-1′), 53.2 (C-6′′), 57.9 (C-1′′′), 63.6 (C-2′′), 82.1 and 83.1 (C-1′′ and C-7′′), 97.2 (C-4′′), 171.01 (C-1), 197.0 (C-3′′), 201.4 (C-5′′) ppm. MS (DIP-CI-NH_3, 70 eV, 150 °C): m/z (%) = 442 (100) $[M + NH_4^+]$, 365 (80) [M – AcO], 297 (26) [M – I]. $C_{15}H_{21}IO_6$ (424.23): calcd. C 42.47, H 4.99; found C 42.58, H 4.87.

(*R*)-{(1*R*,2*S*,6*R*,7*S*)-2,6-Dimethyl-3,5-dioxo-10-oxabicyclo[5.2.1]-dec-2-yl}(methoxy)methyl Acetate (31a): IR (film): $\tilde{\nu}$ = 3359 (O–H, st), 2940 (Csp^3–H, st), 1725 (C=O, st), 1696 (C=O), 1233 (C–O, st), 1109, 1060, 1011 (C–O, st) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.94 (d, J = 6.8 Hz, 3 H, 11′′-H), 1.00 (s, 3 H, 12′′-H), 1.2–1.9 (m, 4 H, 8′′-H and 9′′-H), 2.00 (s, 3 H, 2-H), 3.31 (dq, J = 6.2, J = 6.4 Hz, 1 H, 6′′-H), 3.00 (d, J = 8.0 Hz, 1 H, 4′′-H) 3.59 (s, 3 H, 1′′′-H), 4.29 (dd, J = 7.6, J = 7.6 Hz, 1 H, 1′′-H), 4.40–4.48 (m, 1 H, 7′′-H), 4.57 (d, J = 8.8 Hz, 4′′-H, H), 6.6 (s, 1 H, 1′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 11.6 (C-12′′), 11.6 (C-11′′), 21.1 (C-2), 25.9 and 26.9 (C-8′′ and C-9′′), 54.2 (C-6′′), 57.9 (C-4′′), 58.6 (C-1′′′), 63.1 (C-2′′), 82.8 and 84.0 (C-1′′ and C-7′′), 98.9 (C-1′), 171.1 (C-1), 199.6 (C-3′′), 203.0 (C-5′′) ppm. MS (DIP-CI-NH_3, 70 eV, 150 °C): m/z (%) = 327 (3) [M + C_2H_5]$^+$, 339 (1) [M + C_2H_7]$^+$, 239 (100) [M – AcO]. $C_{15}H_{22}O_6$ (298.33): calcd. C 60.39, H 7.43; found C 60.25, H 7.57.

(*S*)-{(1*R*,2*S*,6*R*,7*S*)-2,6-Dimethyl-3,5-dioxo-10-oxabicyclo[5.2.1]dec-2-yl}(methoxy)methyl Acetate (31b): IR (film): $\tilde{\nu}$ = 3360 (O–H, st), 2945 (Csp^3–H, st), 1724 (C=O, st), 1700 (C=O), 1250 (C–O, st), 1105, 1070 (C–O, st) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.95 (d, J = 7.2 Hz, 3 H, 11′′-H), 1.01 (s, 3 H, 12′′-H), 1.2–2.0 (m, 4 H, 8′′-H and 9′′-H), 2.19 (s, 3 H, 2-H), 3.26–3.34 (m, 1 H, 6′′-H), 3.28 (d, J = 8.8 Hz, 1 H, 4′′-H) 3.39 (s, 3 H, 1′′′-H), 3.99 (dd, J = 7.6, J = 7.6 Hz, 1 H, 1′′-H), 4.40–4.50 (m, 1 H, 7′′-H), 4.53 (d, J = 8.8 Hz, 1 H, 4′′-H), 6.74 (s, 1 H, 1′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 11.5 (C-12′′), 11.4 (C-11′′), 21.1 (C-2), 54.01 (C-6′′), 57.5 (C-4′′), 57.6 (C-1′′′), 63.1 (C-2′′), 82.4 and 83.7 (C-1′′ and C-7′′), 97.6 (C-1′) ppm. MS (DIP-CI-NH_3, 70 eV, 150 °C): m/z (%) = 327 (8) [M + $C_2H_5^+$], 339 (5) [M + $C_2H_7^+$], 239 (100) [M – AcO]. $C_{15}H_{22}O_6$ (298.33): calcd. C 60.39, H 7.43; found C 60.25, H 7.57.

Synthesis of (1*R*,2*S*,6*R*,7*S*)-2,6-Dimethyl-3,5-dioxo-10-oxabicyclo-[5.2.1]decane-2-carbaldehyde (32): Into a 100 mL flask, previously heated under vacuum and purged with argon, compound **25** (100 mg, 0.39 mmol) was placed. Subsequently, LTA (174 mg, 0.39 mmol) and I_2 (99.06 mg, 0.39 mmol) were added all at once under argon. The resulting solid mixture was dissolved in anhydrous benzene (2 mL) and stirred at room temperature for 3.5 h. Once the reaction was complete, the reaction mixture was perco-

lated through a short column of Celite®, eluting with diethyl ether. The organic solution was then concentrated to a volume of 20 mL and subsequently washed with aq. $NaHCO_3$ (1.2 M, 3 × 20 mL), aq. $Na_2S_2O_3$ (5% w/w, 4 × 25 mL) and distilled water (25 mL). The organic fraction was dried with $MgSO_4$, filtered and concentrated to dryness resulting in 130 mg of the crude product. This product was purified by flash column chromatography on silica gel, eluting with mixtures of hexane and diethyl ether of increasing polarity (with H/E, 70:30) to obtain **32** (19.2 mg, 49% yield for a 100% conversion of **25**). IR (film): $\tilde{\nu}$ = 3421, 2978 (Csp^3–H, st), 1718, 1695 (C=O), 1266 (C–O, st), 1133, 1060, 1006 (C–O, st) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.95 (d, J = 6.8 Hz, 3 H, 12′-H), 1.10 (s, 3 H, 11′-H), 1.3 (m, 1 H, 9′-H), 1.8 (m, 1 H, 8′-H), 1.9 (m, 1 H, 8′-H), 2.0 (m, 1 H, 9′-H), 3.29 (d, J = 8.8 Hz, 1 H, 4′-H), 4.54 (d, J = 8.8 Hz, 1 H, 4′-H), 3.27 (m, 1 H, 6′-H), 4.65 (dd, J = 7.8, J = 7.8 Hz, 1 H, 1′-H), 4.4–4.5 (m, 1 H, 7′-H), 9.78 (s, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 11.5 (C-12′), 14.1 (C-11′), 25.7 and 26.6 (C-8′ and C-9′), 54.0 (C-6′), 48.7 (C-1), 60.0 (C-4′), 82.2 and 84.7 (C-1′ and C-7′) ppm. MS (DIP-CI-NH_3, 70 eV, 150 °C): m/z (%) = 225 (100) [M + 1], 253 (15) [M + C_2H_5]$^+$, 265 (7) [M + C_3H_5]$^+$, 195 (23) [M – CHO]. $C_{12}H_{16}O_4$ (224.25): calcd. C 64.27, H 7.19; found C 64.15, H 7.03.

Synthesis of 1,8-Epoxycyclodecanes 33a and 33b: In a 100 mL round-bottomed flask, previously heated under vacuum and purged with argon, compound **27** (134 mg, 0.64 mmol) was placed. Afterwards, LTA (284 mg, 0.64 mmol) and I_2 (162 mg, 0.64 mmol) were added under argon. The solid mixture was dissolved in anhydrous benzene (2 mL) and stirred at room temperature for 30 min. Once the reaction was complete, the reaction mixture was filtered through Celite®, eluting with diethyl ether. The organic solution was concentrated to a volume of 20 mL and successively washed with aq. $NaHCO_3$ (1.2 M, 3 × 20 mL), aq. $Na_2S_2O_3$ (5% w/w, 4 × 25 mL) and distilled water (25 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated to dryness to afford 260 mg of an oily crude product. The product was purified by flash column chromatography on silica gel, eluting with hexane/diethyl ether mixtures of increasing polarity to obtain 94 mg of **33a** (with H/E, 40:60) and 40 mg of **33b** (with H/E, 65:35) in a 76% overall yield for both isomers. Also, 24 mg of starting material **27** was recovered (82% conversion).

(1*S*,2*R*,7*S*,8*R*)-7-Iodo-2,7-dimethyl-11-oxabicyclo[6.2.1]undecane-3,5-dione (33a): IR (film): $\tilde{\nu}$ = 3379 (O–H, st), 2978, 2919 (Csp^3–H, st), 1691 (C=O), 1233 (C–O, st), 1109, 1060, 1019 (C–O, st) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.97 (d, J = 7.2 Hz, 3 H, 12-H), 1.99 (s, 3 H, 13-H), 1.45 (m, 1 H, 9α-H), 1.78 (m, 1 H, 9β-H), 2.00 (m, 1 H, 10β-H), 2.30 (m, 1 H, 10α-H), 2.55 (d, J = 14 Hz, 1 H, 6α-H), 2.76 (d, J = 14 Hz, 1 H, 6β-H), 3.40 (d, J = 12 Hz, 1 H, 4α-H), 3.84 (d, J = 12 Hz, 1 H, 4β-H), 3.48 (dq, J = 5.2, J = 6.9 Hz, 1 H, 2-H), 4.30 (dd, J = 11 Hz, J = 5.8 Hz, 1 H, 8-H), 4.30 (ddd, J = 2, J = 5.2, J = 9.2 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.6 (C-13), 25.7 and 26.01 (C-9 and C-10), 35.0 (C-12), 44.2 (C-7), 48.01 (C-2), 48.7 (C-6), 67.2 (C-4), 82.8 (C-1), 91.6 (C-8), 197.6 (C-5), 209.7 (C-3) ppm. MS (DIP-CI-NH_3, 70 eV, 150 °C): m/z (%) = 365 (1) [M + C_2H_5]$^+$, 337 (27) [M + 1], 209 (100) [M – I]. $C_{12}H_{17}IO_3$ (336.16): calcd. C 42.87, H 5.10; found C 42.95, H 4.97.

(1*S*,2*R*,7*R*,8*R*)-7-Iodo-2,7-dimethyl-11-oxabicyclo[6.2.1]undecane-3,5-dione (33b): IR (film): $\tilde{\nu}$ = 3396 (O–H, st), 2977, 2929 (Csp^3–H, st), 1692 (C=O), 1142, 1045, 1021 (C–O, st) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.96 (d, J = 7.2 Hz, 3 H, 12-H), 2.35 (s, 3 H, 13-H), 1.82 (m, 1 H, 9β-H), 2.25 (m, 2 H, 9α-H, H-10α), 1.97 (m, 1 H, 10β-H), 2.72 (d, J = 14.0 Hz, 1 H, 6α-H), 3.42 (d, J = 14.0 Hz, 1 H, 4α-H), 3.59 (d, J = 12.0 Hz, 1 H, 4β-H), 3.59 (d, J = 12.0 Hz, 1 H, 6β-H), 3.35 (dq, J = 6.5, J = 5.0 Hz, 1 H, 2-H), 4.23 (dd, J = 11.0, J = 5.6 Hz, 1 H, 8-H), 4.34–4.40 (m, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.9 (C-12), 25.0 (C-10), 32.0 (C-9), 35.5 (C-13), 46.8 (C-7), 47.9 (C-2), 50.4 (C-6), 67.01 (C-4), 85.7 (C-8), 88.7 (C-1), 197.9 (C-5), 209.5 (C-3) ppm. MS (DIP-CI-NH_3, 70 eV, 150 °C): m/z (%) = 354 (100) [M + NH_4]$^+$, 337 (27) [M + 1], 209 (13) [M – I]. $C_{12}H_{17}IO_3$ (336.16): calcd. C 42.87, H 5.10; found C 42.91, H 5.24.

Reduction of the C-4 Ketone Group in 25. Synthesis of (1*R*,2*S*,3*S*,4*R*,6*R*,7*R*,8*S*)-3-Ethoxy-2,7-dimethyl-11-oxatricyclo-[6.2.1.0^{2,6}]undecane-4,6-diol (35): In a 25 mL flask, $NaBH_4$ (107.9 mg, 2.86 mmol) was dissolved in anhydrous methanol (1 mL). The system was purged with nitrogen and cooled to 0 °C. Subsequently, compound **25** (120.6 mg) was added by cannula, dissolved in MeOH (1.5 mL). The reaction was monitored by TLC and when complete, 3–4 drops of water were added to quench the excess of $NaBH_4$. After 15 min, the solution was concentrated to dryness by rotary evaporation. The resulting solid was lixiviated with ethyl acetate (8 × 10 mL). The organic extract was dried with anhydrous $MgSO_4$, filtered and concentrated to dryness to obtain product **35** (116.9 mg, 96% yield, 100% conversion of starting material). IR (film): $\tilde{\nu}$ = 3421 (OH, st), 2936, 2888 (C-H, st), 1102, 1075, 1041 (C–O, st) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.86 (d, J = 7.2 Hz, 3 H, 13-H), 0.97 (s, 3 H), 1.25 (t, J = 7.0 Hz, 3 H, 2′-H), 1.55 (dd, J = 14.4, J = 3.6 Hz, 1 H, 5-H), 1.60–1.85 (m, 9-H and 10-H), 2.00–2.10 (m, 9-H and 10-H), 1.70 (m, 1 H, 7-H), 2.40 (dd, J = 14.2, J = 7.8 Hz, 1 H, 5-H), 3.66 (dq, J = 7.0, J = 6.9 Hz, 1 H, 1′-H), 3.68 (dq, J = 7.0, J = 6.9 Hz, 1 H, 1′-H), 3.95 (d, J = 7.6 Hz, 1 H, 1-H), 4.00–4.04 (m, 1 H, 8-H), 4.06–4.12 (m, 1 H, 4-H), 4.30 (d, J = 6.8 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.2 (C-13), 12.5 (C-12), 15.9 (C-2′), 24.1 (C-10), 24.6 (C-9), 41.5 (C-7), 47.6 (C-5), 49.2 (C-2), 66.3 (C-4), 67.2 (C-1′), 78.1 (C-1), 79.7 (C-8), 80.5 (C-3) ppm. MS (DIP-CI-NH_3, 70 eV, 150 °C): m/z (%) = 274 (100) [M + NH_4]$^+$, 257 (69) [M + 1], 239 (60) [M – OH]. $C_{14}H_{24}O_4$ (256.34): calcd. C 65.60, H 9.44; found C 65.72, H 9.55.

Synthesis of (1*R*,2*S*,3*S*,4*R*,6*R*,7*R*,8*S*)-3-Ethoxy-6-hydroxy-2,7-dimethyl-11-oxatricyclo[6.2.1.0^{2,6}]undec-4-yl Acetate (36): In a 50 mL flask, compound **35** (20 mg), pyridine (63 μL), acetic anhydride (73 μL) and a catalytic amount of DMAP were placed and dissolved in anhydrous dichloromethane (0.5 mL). The reaction mixture was stirred under nitrogen at room temperature for 72 h (monitored by TLC until complete conversion). The reaction mixture was cooled to 0 °C and aq. HCl (1 M, 0.5 mL) was added. The solution was stirred for 5 min and then extracted with ethyl acetate (5 × 3 mL). The organic extracts were combined, dried with anhydrous $MgSO_4$, filtered and concentrated to dryness to obtain product **36** (27.2 mg, quantitative yield, 100% conversion of **35**). IR (film): $\tilde{\nu}$ = 3453 (OH, st), 2936 (C–H, st), 1740 (C=O, st), 1244, 1105, 1043 (C–O, st) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.87 (d, J = 7.2 Hz, 3 H, 13′-H), 0.99 (s, 3 H, 12′-H), 1.13 (t, J = 7.0 Hz, 3 H, 2′′-H), 1.55 (dd, J = 14.6, J = 3.8 Hz, 1 H, 5′-H), 1.66–1.74 (m, 9′-H), 1.70 (m, 1 H, 7′-H), 2.02–2.16 (m, 9′-H and 10′-H), 2.07 (s, 3 H, 2-H), 2.45 (dd, J = 14.8, J = 8.4 Hz, 1 H, 5′-H), 3.49 (dq, J = 9.6, J = 6.9 Hz, 1 H, 1′′-H), 3.58 (dq, J = 9.2, J = 7.1 Hz, 1 H, 1′′-H), 3.95 (d, J = 7.6 Hz, 1 H, 1′-H), 4.04 (dd, J = 7.6 Hz, 1 H, 8′-H), 4.27 (d, J = 7.2 Hz, 1 H, 3′-H), 5.18–5.25 (m, 1 H, 4′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.1 (C-13′), 12.01 (C-12′), 15.7 (C-2′′), 21.3 (C-2), 24.1 (C-9′), 24.6 (C-10′), 41.4 (C-7′), 45.1 (C-5′), 49.3 (C-2′), 67.2 (C-1′′), 69.4 (C-4′), 77.7 (C-1′), 79.5 (C-8′), 79.8 (C-3′), 170.7 (C-1) ppm. MS (DIP-CI-NH_3, 70 eV, 150 °C): m/z (%) = 316 (9) [M + NH_4]$^+$, 299 (100)

[M + 1], 239 (62) [M – OAc]. $C_{16}H_{26}O_5$ (298.37): calcd. C 64.41, H 8.78; found C 64.54, H 8.91.

Synthesis of (1*R*,2*R*,3*R*,4*R*,7*R*,8*S*)-3-Ethoxy-2-iodo-2,7-dimethyl-6-oxo-11-oxabicyclo[6.2.1]undec-4-yl Acetate (37): In a 100 mL round-bottomed flask, previously heated under vacuum and purged with argon, compound **36** (25.5 mg, 0.86 mmol), LTA (37.9 mg, 0.86 mmol) and I_2 (21.7 mg, 0.86 mmol) were placed. The solid mixture was dissolved in anhydrous benzene (1 mL), and the resulting solution was stirred at room temperature for 3 h. Once the reaction was complete (monitored by TLC), the reaction mixture was filtered through a short pad of Celite® in a column, eluting with diethyl ether. The volume of the ethereal solution was reduced to 20 mL and successively washed with aq. $NaHCO_3$ (1.2 M, 3 × 20 mL), aq. $Na_2S_2O_3$ (5% w/w, 4 × 25 mL) and distilled water (25 mL). The organic phase was dried with anhydrous $MgSO_4$, filtered and concentrated to dryness to afford 119.4 mg of crude product. The product was purified by flash column chromatography on silica gel, eluting with mixtures of hexane and diethyl ether of increasing polarity (with H/E, 60:40) to obtain 27.1 mg of **37** (75% yield for a 100% conversion of **36**). IR (film): $\tilde{\nu}$ = 2975, 2930 (C–H, st), 1740, 1703 (C=O, st), 1238, 1074, 1047, 1020 (C–O, st) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.94 (d, J = 7.2 Hz, 3 H, 13′-H), 1.24 (t, J = 7 Hz, 3 H, 2′′-H), 1.66–1.75 (m, 1 H, 10′-H), 1.84–2.07 (m, 2 H, 9′-H and 10′-H), 2.09 (s, 3 H, 12′-H), 2.09 (s, 3 H, 2-H), 2.21 (dd, J = 11.8, J = 7.0 Hz, 1 H, 9′-H), 2.66–2.78 (m, 1 H, 5′-H), 3.45–3.54 (m, 1 H, 7′-H), 3.56 (dq, J = 9.2, J = 7.0 Hz, 2 H, 1′′-H), 3.72 (dq, J = 9.2, J = 7.1 Hz, 1 H, 1′′-H), 4.02 (br. s, 1 H, 3′-H), 4.13–4-17 (m, 1 H, 8′-H), 4.24–4.29 (m, 1 H, 1′-H), 6.92–6.96 (m, 1 H, 4′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.1 (C-13′), 15.2 (C-2′′), 21.7 (C-2), 26.3 (C-10′), 26.8 (C-10′), 31.0 (C-12′), 49.8 (C-7′), 50.5 (C-5′), 55.6 (C-2′), 69.6 (C-1′′), 71.8 (C-4′), 81.9 (C-8′), 89.8 (C-1′), 92.2 (C-3′), 169.8 (C-1), 211.4 (C-6′) ppm. MS (DIP-CI-NH_3, 70 eV, 150 °C): m/z (%) = 442 (96) $[M + NH_4]^+$, 425 (25) [M + 1], 365 (60) [M – OAc], 297 (19) [M – I]. $C_{16}H_{25}IO_5$ (424.27): calcd. C 45.29, H 5.94; found C 45.41, H 5.86.

Supporting Information (see footnote on the first page of this article): Tables S1 and S2 contain selected bond lengths and bond angles for compounds **25**, **28a**, **32** and **37**. The numbering of carbon atoms in these tables follows the IUPAC nomenclature.

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