



## ORIGINAL ARTICLE

# Stereoselectivity of the captodative alkenes 1-acetylvinyl arenecarboxylates in Diels-Alder reactions with cyclic dienes and stereospecific rearrangement of their bicyclo[2.2.n] $\alpha$ -ketol adducts



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Received 28 March 2017; accepted 13 August 2017  
Available online 1 September 2017

## KEYWORDS

Captodative alkenes;  
1-Acetylvinyl *p*-nitrobenzoyloxy;  
 $\alpha$ -Keto carbinols;  
 $\alpha$ -Ketol rearrangement;  
Cascade process;  
mCPBA

**Abstract** Captodative alkene 1-acetylvinyl *p*-nitrobenzenecarboxylate **1a** was evaluated for its reactivity and stereoselectivity with cyclohexadiene (**10**) in Diels-Alder reactions, showing exclusive *endo* preference. The two hydrolyzed products of the *endo* and the *exo* adducts obtained from the Diels-Alder cycloaddition between **1a** and cyclopentadiene (**7**) were **8b** and **9b**. When treated with mCPBA, a ring expansion took place to stereospecifically yield the novel 3-oxatricyclo[3.3.1.0<sup>2,4</sup>]nonanone acyloins **15** and **16**, respectively. In the case of the  $\alpha$ -ketol bicyclo[2.2.2]octanes **11b** and **12b**, the epoxidation/Baeyer-Villiger cascade process was preferred, resulting in the *syn* ketooxide **19b** from each isomer. A synthetic application of this kind of transformation was carried out by reacting ketols **8b** and **9b** with an excess of mCPBA through a five-step cascade process to yield the bicyclic lactone **27** as a potential precursor of racemic  $\beta$ -carbaxlyose.

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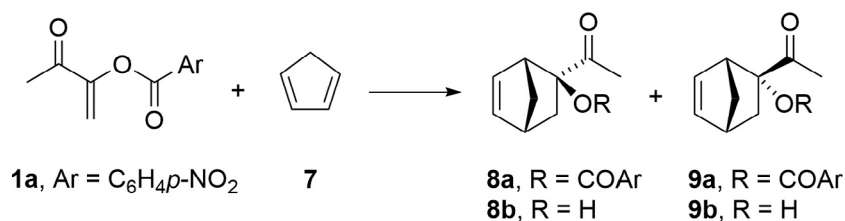


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## 1. Introduction

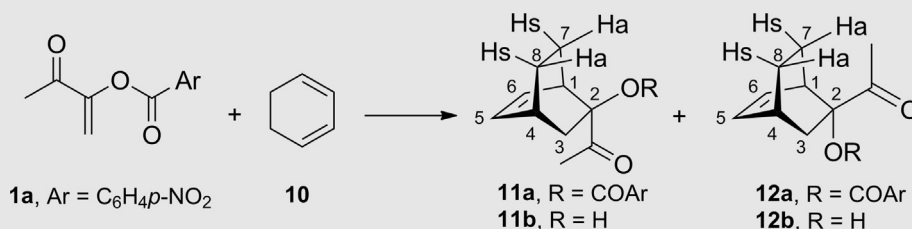
Diels-Alder reactions are one of the fundamental cornerstones in organic chemistry for the experimental and theoretical study of concerted reactions (Sauer and Sustmann, 1980; Herges et al., 1994; Damoun et al., 1997; Brocksom et al., 2001; Tantillo et al., 2001; Wang et al., 2009; Domingo et al.,





**Scheme 2** Preparation of adducts **8a-9a** via Diels-Alder addition of captodative alkene **1a** to cyclopentadiene (**7**), and structures of the  $\alpha$ -keto derivatives **8b** and **9b**.

**Table 1** Diels-Alder reactions of captodative olefin **1a** with cyclohexadiene (**10**).<sup>a</sup>



Entry	Solvent	Catalyst (mol equiv)	T (°C)	t (h)	<b>11a/12a</b> (ratio) <sup>b</sup>	Yield (%) <sup>c</sup>
1	C <sub>6</sub> H <sub>6</sub>	–	130	168	100:0	70
2	CH <sub>2</sub> Cl <sub>2</sub>	TiCl <sub>4</sub> (8.6)	–50	3	44:56	92
3	CH <sub>2</sub> Cl <sub>2</sub>	BF <sub>3</sub> Et <sub>2</sub> O (19)	–50	10	67:33	85
4	CH <sub>2</sub> Cl <sub>2</sub>	AlCl <sub>3</sub> (2.4)	0	1	100:0	95
5	CH <sub>2</sub> Cl <sub>2</sub>	ZnI <sub>2</sub> (24)	25	120	100:0	84

<sup>a</sup> All under N<sub>2</sub> atmosphere, with 2.5 mol equiv of **10**, and with 0.01 mol equiv of hydroquinone for the thermal trial.

<sup>b</sup> Determined by <sup>1</sup>H NMR from the reaction crudes.

<sup>c</sup> After column chromatography.

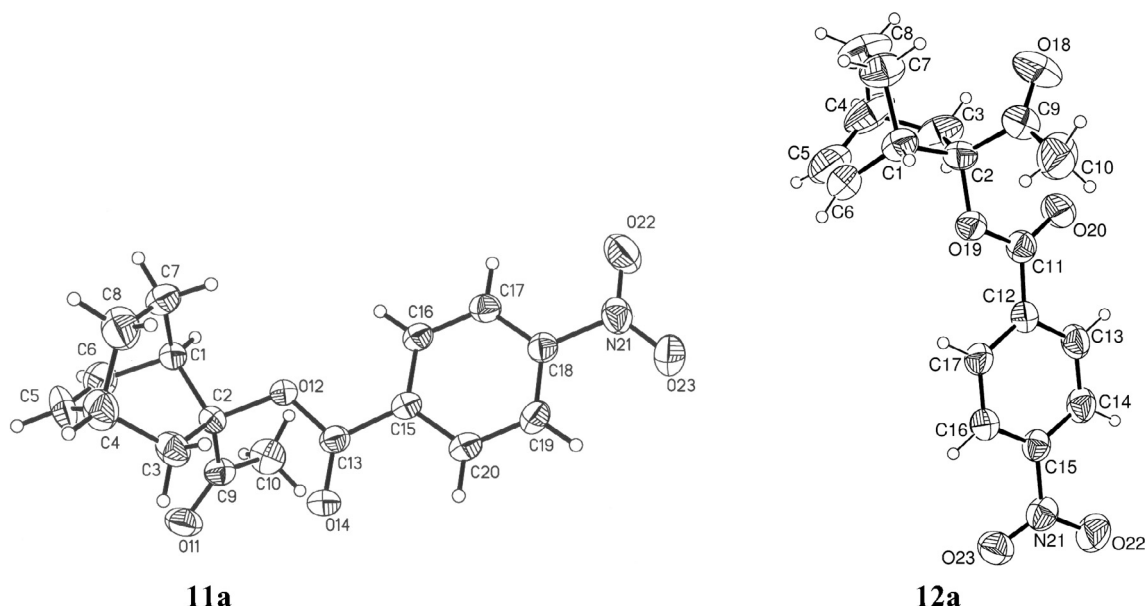
AlCl<sub>3</sub> or ZnI<sub>2</sub> as the catalyst. Indeed, the *endo* isomer **11a** was isolated as a single product (Table 1, entries 4 and 5).

The amount of Lewis acids (shown in Table 1) was optimized to render the cycloadditions in the shortest reaction times. A large excess of Lewis acid was used in most cases, since the reaction time sharply increased with a lesser amount. It is likely that the multiple binding sites (oxygen atoms) can explain the need for such large catalyst loads. Regarding AlCl<sub>3</sub>, interestingly, only 2.4 mol equiv of the solid catalyst were required, and the ratio of the *endo/exo* adducts was not significantly modified by using greater amounts of this catalyst.

Besides identifying the most efficient trials (Table 1), several screening tests were carried out to determine the optimal reaction conditions, taking into account the catalyst, temperature and reaction time. As previously mentioned, the type of Lewis acid catalyst modifies reactivity and diastereoselectivity (Table 1). Although both temperature and reaction time affected the yields, the *endo/exo* diastereoselective ratio was not significantly modified by these factors. For example, when the TiCl<sub>4</sub>-catalyzed reaction took place at a temperature higher than –50 °C, there was a decomposition of the dienophile and the formation of a complex mixture of products. By reducing the temperature to –78 °C, the reaction time was extended

5–6 h with no considerable change of the *endo/exo* ratio. Likewise, by employing AlCl<sub>3</sub> and ZnI<sub>2</sub> as the catalysts at temperatures lower than those indicated in Table 1 (entries 4 and 5), either the cycloaddends did not react or the reaction time was longer, but the *endo/exo* ratios remained essentially the same. Similar behavior was observed for the thermal trials, in which a reaction temperature below or above 130 °C, augmented or diminished the reaction times, respectively. However, the yields and *endo/exo* ratios were comparable regardless of the temperature.

The structure of the major *endo* stereoisomer **11a** was established by X-ray diffraction analysis (Fig. 2). Notably, the conformation of the acetyl group is such that the carbonyl group is oriented towards the C-3 methylene of the bicyclo[2.2.2]oct-5-ene (*in* conformation). An identical conformation is found in the *endo* adduct **8a** (García de Alba et al., 1996). The minor *exo* adduct **12a** was separated from the reaction mixture by column chromatography and was fully characterized by spectroscopy, elemental analysis and X-ray crystallography (Fig. 2). In the latter structure, the carbonyl group is also oriented towards the C-3 methylene of the bicyclo[2.2.2]oct-5-ene. This conformation seems to be adopted even in solution, as suggested by the <sup>1</sup>H NMR high frequency chemical shift of the H-C3 proton *syn* to the carbonyl group in both adducts:



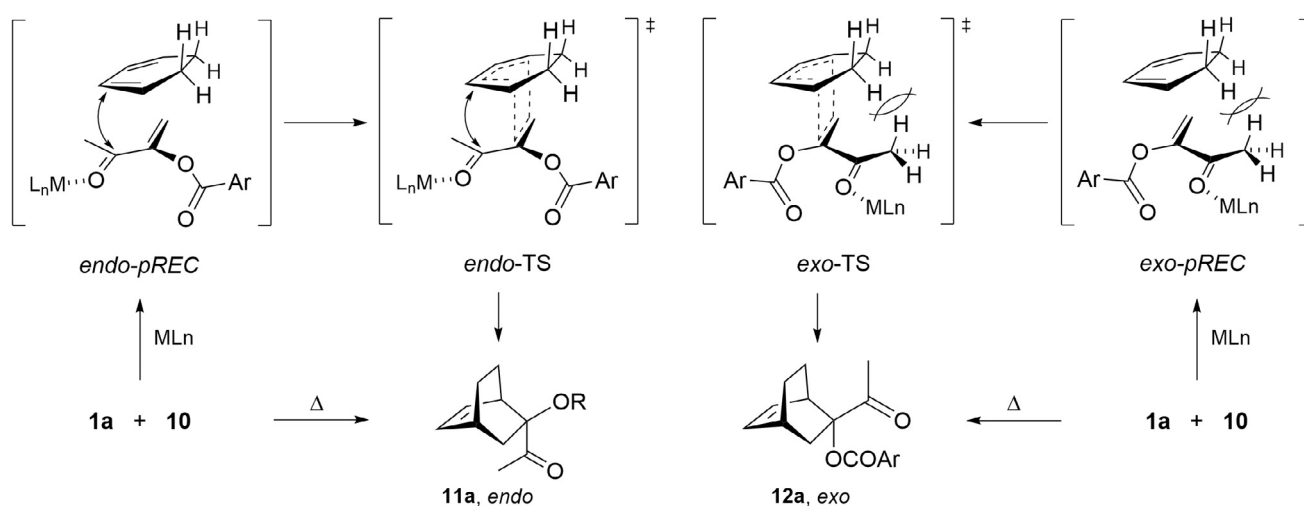
**Fig. 2** X-ray structures of the *endo* adduct **11a** and *exo* adduct **12a** (ellipsoids with 30% probability).

2.48 ppm for H-3n of **11a** (1.59 ppm for H-3x) and 2.90 ppm for H-3x of **12a** (1.33 ppm for H-3n). The proximity of the oxygen atom of the carbonyl group probably generates a deshielding effect on the *syn* protons.

The observed *endo* diastereoselectivity for the thermal and some of the catalyzed trials could possibly be explained by steric interactions of the acetyl and the aryloxy groups with the most hindered ethane bridge of the diene (**Fig. 3**). According to the X-ray diffraction and quantum calculations of **1a** (Jiménez-Vázquez et al., 1997), the *s-trans* conformation is preferred by the conjugated enone system, with the *p*-nitrobenzoyl group out of the plane formed by the enone moiety. This preferred conformation probably is also adopted at the ground-state complexes of **1a** with Lewis acids, including  $\text{AlCl}_3$  and  $\text{ZnI}_2$  (Loncharich et al., 1987; Denmark and Almstead, 1993; Ishihara et al., 1993), as well as at the transition states

(Rebiere et al., 1990; Maruoka et al., 1994). Therefore, the *exo* approach would be prevented by non-bonding repulsive interactions of the methyl group and the bulky metal-coordinated carbonyl group with the ethane bridge. Additionally, at the *endo* transition state, the  $\pi$ -systems might be stabilized by secondary interactions, such as those promoted by orbitals (Arrieta et al., 2001; Caramella et al., 2002; Wannere et al., 2007) or by electrostatic forces (García et al., 2000; Sakata and Fujimoto, 2016).

In agreement with previous results (Suárez and Sordo, 1998), we have recently demonstrated the importance of the formation of *pre-reactive electrostatic complexes* (*pREC*) in the thermal Diels-Alder potential energy surfaces (PES). These complexes are a result of the  $\pi/\pi$  interaction between the reactants (Ramírez-Gualito et al., 2013), which is mainly controlled by dispersion forces (Cioslowski et al., 1993). These



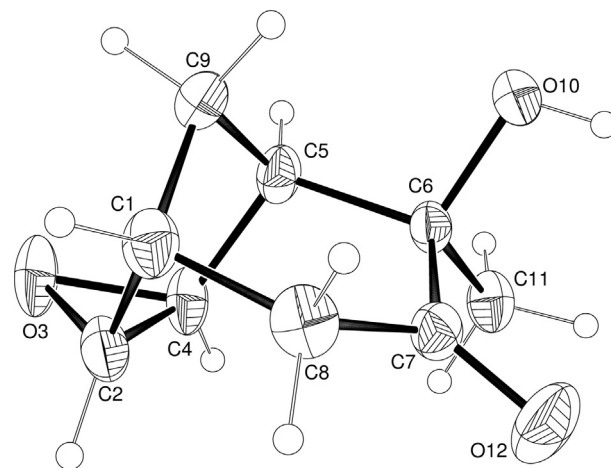
**Fig. 3** Possible interactions at the *endo* and *exo* *pREC*s and TSs between the  $\text{ML}_n$  ( $n = 2, 3$ )-complexed and non-complexed dienophile **1a** and cyclohexadiene (**10**).

are to a great extent responsible for the *endo* preference (Ramírez-Gualito et al., 2013). It is likely that similar *p*RECs are formed in the presence of the Lewis acid catalyst, and that repulsive steric interactions are present at the *exo-p*REC. Such interactions would then destabilize not only this complex but its respective transition state (*exo*-TS) as well. Hence, the secondary interactions and dispersion forces stabilizing the *endo-p*REC may also stabilize the *endo*-TS, leading to the selective formation of the *endo* adduct **11a**.

### 2.2. Stereospecific rearrangement of $\alpha$ -ketols **8b** and **9b**

$\alpha$ -Ketols **8b** and **9b** were prepared by saponification ( $K_2CO_3$ , MeOH, reflux, 10 h) of the corresponding adducts **8a** and **9a** in almost quantitative yields. Treatment of  $\alpha$ -ketol **8b** with 1.0 mol equiv of mCPBA in  $CH_2Cl_2$  at room temperature led exclusively to the *endo*-hydroxy-*exo*-epoxy tricyclo[3.3.1.0<sup>2,4</sup>]nonan-7-one (*endo*-hydroxy- $\alpha$ -ketol) **15**, in 68% yield (Scheme 3). Although analogous bicyclo[2.2.1]  $\alpha$ -ketols have given rise to the corresponding bicyclo[3.2.1] products through an  $\alpha$ -ketol rearrangement (Paquette and Hofferberth, 2003), they do so by undergoing thermal or base-promoted processes under much more severe conditions (Stevens et al., 1972). In these cases, the stereoisomeric ratio of the bicyclo[3.2.1] products depends on the reaction conditions (Creary et al., 1985). The easy rearrangement of  $\alpha$ -ketol **8b** is probably associated with the strain on the ring systems brought about by epoxidation to give the epoxy intermediate **13**. That is, the C–C bond migration might be accelerated to relieve the strain and furnish **15** (Brunner et al., 2001). This process may also be catalyzed by the acidic reaction medium generated both by mCPBA and the *m*-chlorobenzoic acid byproduct of the reaction.

These results suggest that the process is not stereoselective, but instead stereospecific. Indeed, when the *exo*- $\alpha$ -ketol **9b** was submitted to a reaction under identical conditions, only *exo*-hydroxy-*exo*-epoxy tricyclo[3.3.1.0<sup>2,4</sup>]nonan-7-one (*exo*-hydroxy- $\alpha$ -ketol) **16** was obtained, with a 65% yield (Scheme 3). The rearrangement may owe itself to the formation of the corresponding epoxy intermediate, in this case **14**. The structure of *exo*-hydroxy- $\alpha$ -ketol **16** was unambiguously established by X-ray crystallography (Fig. 4), while the structure of *endo*-hydroxy- $\alpha$ -ketol **15** was determined by nOe and 2D NMR experiments. Interestingly, epoxidation takes place

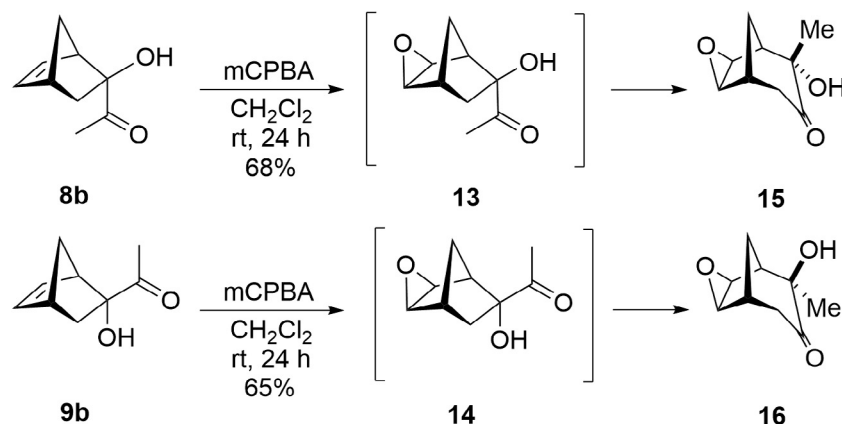


**Fig. 4** X-ray structure of *exo*-hydroxy- $\alpha$ -ketol **16** (ellipsoids with 30% probability).

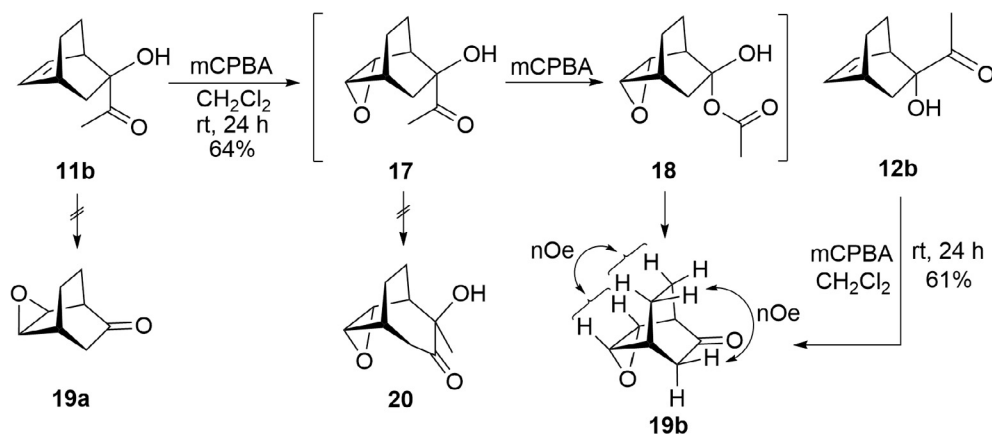
diastereoselectively on the *exo* face of the double bond, regardless of the stereochemistry of  $\alpha$ -ketols **8b** and **9b**.

### 2.3. Rearrangement of $\alpha$ -ketols **11b** and **12b**

Adducts **11a** and **12a** were hydrolyzed under basic conditions ( $K_2CO_3$ , MeOH/THF, reflux, 3–4 h) to afford  $\alpha$ -ketols **11b** and **12b**, respectively, in good yields (81–94%). Reaction conditions analogous to those previously applied for **8b** and **9b** were used for the rearrangement of  $\alpha$ -ketol **11b**. Thus, upon reacting a solution of **11b** in  $CH_2Cl_2$  with 2.0 mol equiv of mCPBA, the *syn*-facial bicyclic ketoepoxide **19b** was produced in 64% yield (Scheme 4). In contrast to the results when utilizing  $\alpha$ -ketols **8b** and **9b**, only the *syn*-ketoepoxide **19b** was formed with **11b**, even in the presence of an excess of mCPBA. No *syn*-epoxyketol **20** was found. Interestingly, the *anti*-facial isomer **19a** was not detected by  $^1H$  NMR analysis of the reaction crude. Under similar reaction conditions,  $\alpha$ -ketol **12b** was also able to exclusively provide **19b**. Ketoepoxide **19b** is presumably generated from a reaction sequence starting with the epoxidation of **11b** to give **17**, followed by the Baeyer-Villiger rearrangement and then the decomposition of the hemiketal **18**. The structure of **19b** was established by nOe experiments showing the relative configuration of the epoxy



**Scheme 3** Epoxidation and stereospecific  $\alpha$ -ketol rearrangement cascade reaction of  $\alpha$ -ketols **8b** and **9b**.



**Scheme 4** Epoxidation/Baeyer-Villiger cascade reaction of  $\alpha$ -ketols **11b** and **12b**.

and keto groups within the bicyclo[2.2.2]octane framework. Therefore, the Baeyer-Villiger reaction was preferable to the possible rearrangement of the  $\alpha$ -ketol **17**, which would have induced the expansion of the bicyclo[2.2.2]octane to afford the bicyclo[3.2.2]nonane derivative **20**.

Hence,  $\alpha$ -ketol **11b** behaves mostly as a  $\beta,\gamma$ -unsaturated carbonyl compound, as we have found for unconjugated cyclohexenones (Ochoa et al., 1999). In the same sense, it is noteworthy that **19b** did not undergo a subsequent Baeyer-Villiger reaction, even though there was an excess of the reagent.

Detailed studies by Ohwada and coworkers (Ohwada et al., 1996) on the stereofacial control of the epoxidation of mono-substituted bicyclo[2.2.2]oct-5-ene derivatives showed that epoxidation was favored on the *syn* face when employing *exo* electron-withdrawing groups, but that this preference decreased with electron-donating groups. The selectivity appears to be controlled by the perturbation of the  $\sigma$  bicyclo[2.2.2]oct-5-ene skeleton on the  $\pi$  double bond (Ohwada, 1999). In the case of the *exo*-isomer **12b**, consequently, epoxidation seems to be controlled by the electron-demand of the acetyl group. Since using **11b** in the reaction also leads to *syn*-epoxide **19b**, it can be understood that the *exo* hydroxyl group and/or the *endo* acetyl group are probably acting as dominant  $\sigma$  electron-withdrawing groups, reinforcing the *syn* selectivity. Anchimeric assistance of the lone pairs of the acetyl or the hydroxyl groups, controlling the *endo* approach of the peroxyacid reagent, cannot be ruled out as another factor (Chamberlain et al., 1970; Hudlicky, 1990; Houk et al., 1997).

Vogel and coworkers (Fattori et al., 1993) also investigated kinetically controlled facial selectivity in reactions between substituted bicyclo[2.2.2]oct-5-en-2-ones and diverse electrophiles. They reported that the approach of the electrophile takes place with *anti* preference in relation to the oxo-substituted tether side, a behavior opposite to what was observed with isomers **11b** and **12b**. Thus epoxidation seems to occur before the Baeyer-Villiger/hydrolysis cascade reaction takes place to furnish the oxo group. Otherwise, the latter would direct the epoxidation towards the formation of the *anti* epoxide **19a**.

These results reveal the synthetic potential of the captodative alkene **1a** as an efficient ketene analogue in the formation of the bicyclo[2.2.1]heptan-2-one and bicyclo[2.2.2]octan-2-one frameworks, similar to other alkenes in Diels-Alder

cycloadditions (Cantello et al., 1974; Trost and Tamaru, 1977; Viehe et al., 1985; Reymond and Vogel, 1990; Kernen and Vogel, 1995).

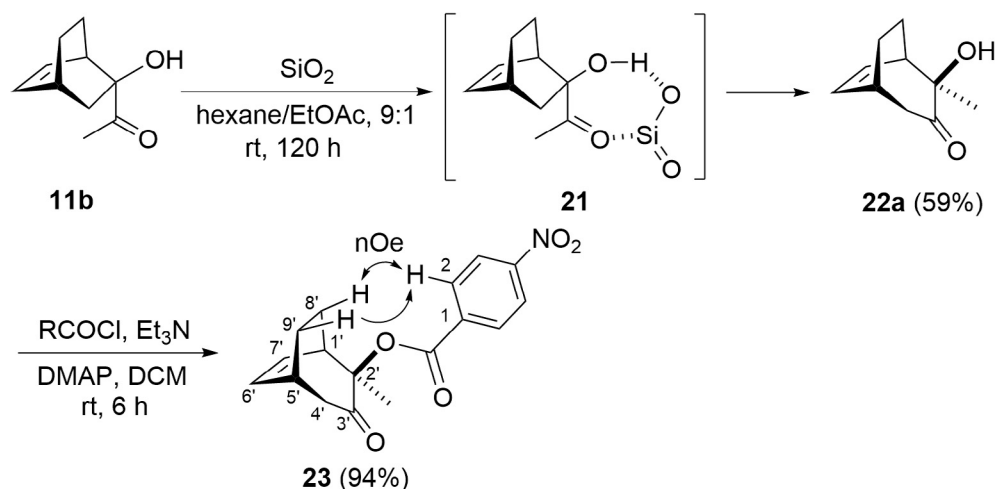
Additionally, we investigated the viable conditions that could lead to the acyloin rearrangement of **11b**, finding that by maintaining the latter in a chromatography column over silica gel at room temperature for 120 h and eluting it with a mixture of hexane/EtOAc (9:1), the expansion product **22a** was isolated as a single isomer (Scheme 5). The structure of the latter was determined by nOe experiments of the 4-nitrobenzoyl derivative **23**, in which the signal size of the methylene protons H-8' and H-9' exhibited enhancements by irradiation of the aromatic H-2 protons.

Notably, the stereoselectivity of this rearrangement was opposite to that found in the bicyclo[2.2.1]hept-5-ene of  $\alpha$ -ketols **8b** and **9b**. In the case of the *endo*  $\alpha$ -ketol **8b** (with the acetyl group on the *endo* side) the expansion leads to *endo*-hydroxy- $\alpha$ -ketol product **15** (with the hydroxyl group on the *endo* side), whereas *exo* **9b** rearranges to the *exo*-hydroxy- $\alpha$ -ketol **16**. Contrarily, the *endo*  $\alpha$ -ketol **11b** provides the *exo* expansion product **22a**. A coordination chelate like **21** could be involved in promoting such inverse stereoselectivity (Creary et al., 1985).

Unexpectedly, unchanged starting material was recovered when  $\alpha$ -ketol **12b** was treated under these conditions. By employing a more severe reaction temperature and longer reaction time, a mixture of starting material and several byproducts was isolated.

#### 2.4. Cascade conversion of $\alpha$ -ketols **8b** and **9b** into the bicyclic $\gamma$ -lactone **26** and a synthetic approach to racemic $\beta$ -carbaxylase

The substituted bicyclo[2.2.1]-5-hepten-2-ones and bicyclo[2.2.1]-5-heptenes have proven to be versatile scaffolds in the synthesis of cyclic and acyclic natural and unnatural products (Corey et al., 1970; Greene et al., 1980; Grieco et al., 1982; Carreño, 1995; Mehta and Islam, 2002; Araki et al., 2003; Vincent et al., 2013). These bicyclic precursors have been obtained from stereoselective and/or regioselective Diels-Alder cycloadditions with substituted cyclopentadienes (Carruthers, 1990; Fringuelli and Taticchi, 2002), including the asymmetric version (Hudon et al., 2008; Reymond and Cossy, 2008; Mukherjee and Corey, 2010; Mehta and Shinde, 2012). Being inspired by these antecedents, we investi-



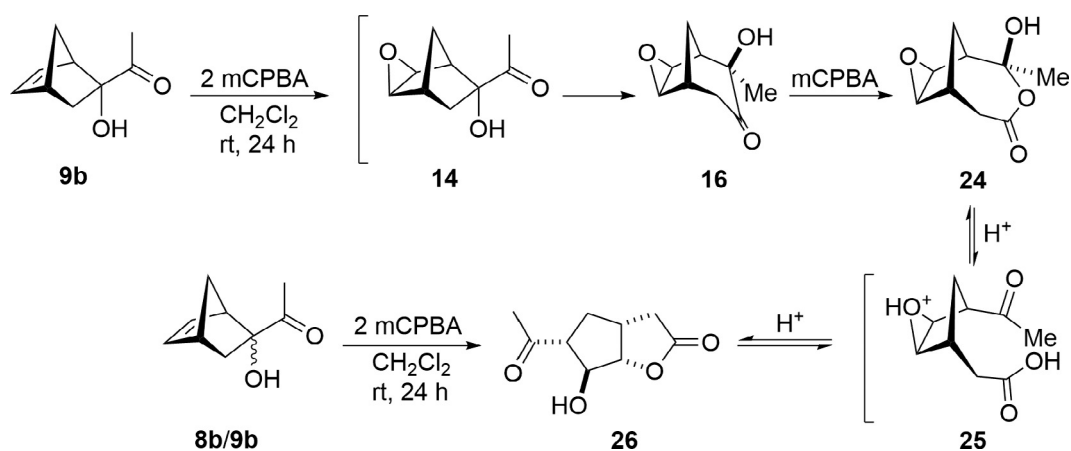
**Scheme 5** Possible stereospecific  $\alpha$ -ketol rearrangement of **11b**.

gated the synthetic potential of  $\alpha$ -ketols **8b** and **9b** and their stereospecific rearrangement in the presence of mCPBA.

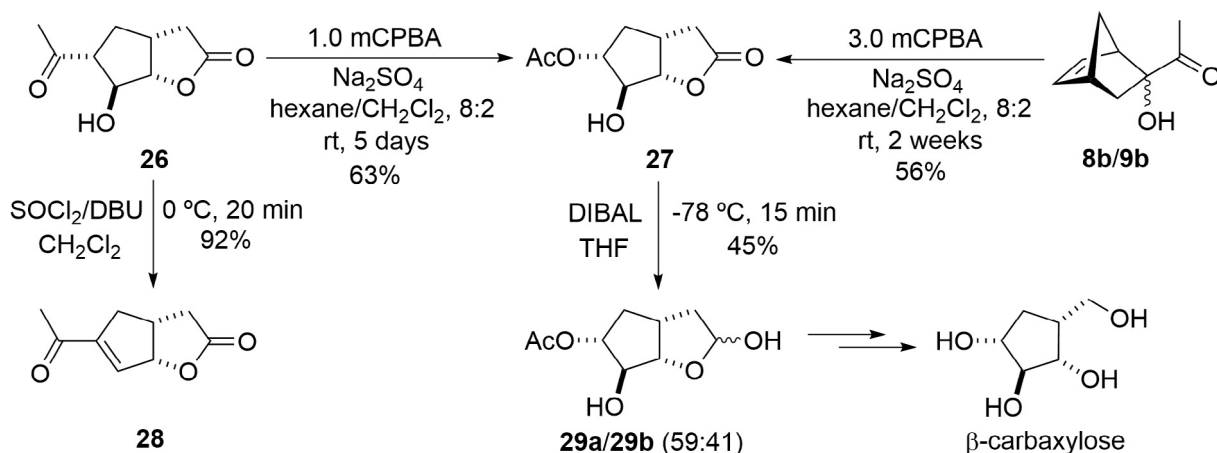
As shown, the treatment of  $\alpha$ -ketols **8b** and **9b** with 1.0 mol equiv of mCPBA in  $\text{CH}_2\text{Cl}_2$  at room temperature resulted in the tricyclo[3.3.1.0<sup>2,4</sup>] derivatives **15** and **16**, respectively (Scheme 3). Furthermore, the reaction of **9b** with 2.0 mol equiv of mCPBA generated the bicyclic  $\gamma$ -lactone **26** as a single diastereoisomeric product in 45% yield (Scheme 6). Similarly, when the reaction was carried out with a mixture of **8b/9b**, compound **26** was isolated as the only product in 70% yield. This transformation likely takes place through a cascade process involving the isolated expanded tricyclo[3.3.1.0<sup>2,4</sup>] epoxy intermediate **16**, which undergoes a Baeyer-Villiger reaction to afford lactone **24**. The regioselectivity of the latter rearrangement may be due to the higher migratory aptitude of the carbinol tertiary center in relation to the methylene group (Krow, 1993; Renz and Meunier, 1999). Lactone **24** is hydrolyzed within the acidic reaction medium, followed by the intramolecular proton-assisted opening of the epoxy group of **25**, promoting stereoselective lactonization to yield the five-membered lactone **26**.

Carbasugars are hydrolysis-resistant analogues to carbohydrates with significant pharmacological activity (Arjona et al.,

2007; Kurteva and Afonso, 2009). In particular, lactone **26** may be a potential precursor of racemic  $\beta$ -carboxylose (Marschner et al., 1995). In order to propose a synthetic approach to the latter compound, we investigated the reactivity of **26** under diverse reaction conditions. Thus, the conversion of the acetyl group into the acetoxy group was carried out through a further Baeyer-Villiger reaction to give  $\gamma$ -lactone **27**. For this purpose, attempts were made using various solvents ( $\text{CH}_2\text{Cl}_2$ ,  $\text{CHCl}_2\text{CHCl}_2$ , MeOH, *tert*-BuOH, THF and  $\text{C}_6\text{H}_6$ ), catalysts (TFA, TFA- $\text{H}_2\text{O}_2$  and *p*-TsOH), temperatures (25–70 °C), and other peracids (mCPBA, mono-*o*-perftalic acid and pertrifluoroacetic acid) (Krow, 1993; Renz and Meunier, 1999). In each case, however, low yields of **27** were obtained. Unexpectedly, a better conversion occurred when the reaction was induced with mCPBA in a mixture of hexane/ $\text{CH}_2\text{Cl}_2$  (8:2) employing a desiccant additive ( $\text{Na}_2\text{SO}_4$ ) at room temperature (Scheme 7). The reduced reactivity of **26** may be due to the steric hindrance found at the acetyl group, which is located at the crowded *endo* face of the bicyclo[3.3.0]oxaoctane. Since the concerted Baeyer-Villiger rearrangement takes place through a bulky transition state (Mihovilovic et al., 2004), the abated reactivity of **26** is understandable.



**Scheme 6** Conversion of  $\alpha$ -ketols **8b** and **9b** into the bicyclic  $\gamma$ -lactone **26**.



**Scheme 7** Conversion of  $\alpha$ -ketols **8b/9b** and bicyclic  $\gamma$ -lactone **26** into bicyclic  $\gamma$ -lactone **27**, as a synthetic approach to racemic  $\beta$ -carboxylose, and into bicycle **28**.

These reaction conditions also efficiently furnished **27** from a mixture of  $\alpha$ -ketols **8b/9b**, although a long reaction time (2 weeks) was required. Despite the modest yield of  $\gamma$ -lactone **27**, it is noteworthy that this conversion involved a least five-steps in a cascade process.

Further reactions carried out on  $\gamma$ -lactone **26** are summarized in **Scheme 7**. When **26** was reacted with thionyl chloride, enone **28** was obtained in high yield. Because lactone **27** is a potential precursor of  $\beta$ -carboxylose (Marschner et al., 1995), the lactone group was reduced with DIBAL, generating a mixture of ketals **29a/29b** (59:41).

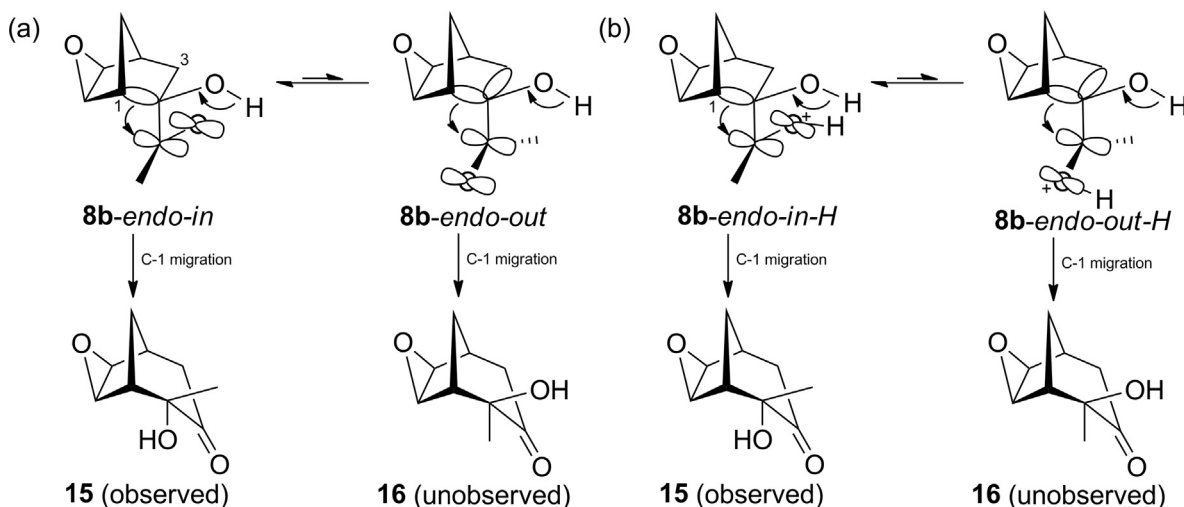
### 2.5. Mechanism of the stereospecific acyloin rearrangement of $\alpha$ -Ketols **8b** and **9b**

Since we have established that the acyloin rearrangement of  $\alpha$ -ketol **8b** stereospecifically produces  $\alpha$ -ketol **15** (**Scheme 3**), a plausible mechanism can be postulated for the C-1 migration pathway of the two possible acetyl group conformations, **8b-endo-in** and **8b-endo-out** (**Scheme 8(a)**). The NMR and

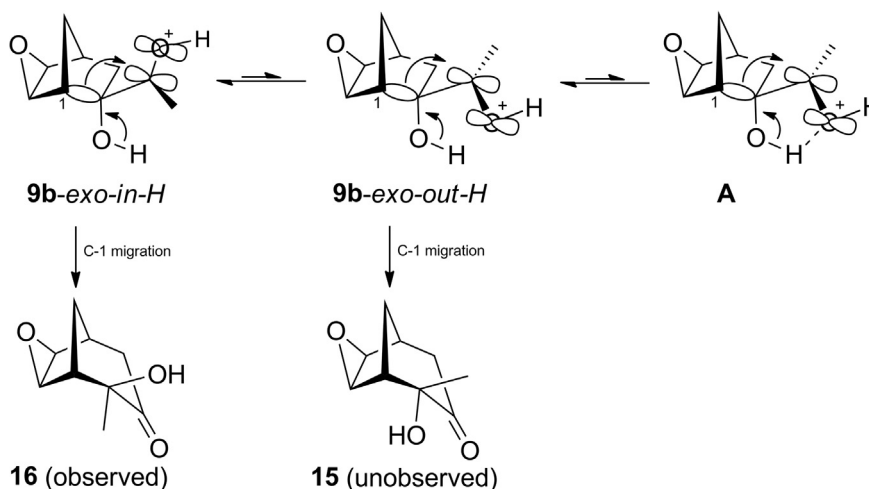
X-ray analyses provided evidence of lower stability for the latter versus former conformation (García de Alba et al., 1996). From this ground state conformational bias, similar conformations are possibly maintained at the transition state with the most stable TS corresponding to **8b-endo-in**, which results in the observed  $\alpha$ -ketol **15**.

Considering that the process is carried out under acidic conditions, a Brønsted acid-catalyzed acyloin rearrangement may also take place (Paquette and Hofferberth, 2003). In such case, both **8b-endo-in** and **8b-endo-out** conformations would be protonated at the carbonyl group (**Scheme 8(b)**), leading to the corresponding TSs with a relative stability similar to that of the neutral species. Therefore, the greater stability of the **8b-endo-in-H** TS would afford  $\alpha$ -ketol **15**.

Regarding *exo*  $\alpha$ -ketol **9b**, the NMR analysis (García de Alba et al., 1996) also suggests that the ground state conformer **9b-exo-in** would be more stable than **9b-exo-out**. Presumably, the protonated species **9b-exo-in-H** and **9b-exo-out-H** and their corresponding transition states would display parallel stability (**Scheme 9**). The TS would be more stable for the former spe-



**Scheme 8** (a) Conformational equilibrium in the neutral species of conformers **8b-endo-in** and **8b-endo-out**, and possible C-1 migration products **15** and **16**. (b) Conformational equilibrium in the protonated species of conformers **8b-endo-in-H** and **8b-endo-out-H**, and possible C-1 migration products **15** and **16**.



**Scheme 9** Conformational equilibrium in the protonated species of conformers **9b-exo-in-H** and **9b-exo-out-H**, and possible C-1 migration products **15** and **16**.

cies than latter species, promoting the formation of the observed  $\alpha$ -ketol **16**. Some reports claim that the controlling factor for the TS is the proton transfer from the hydroxyl group to the oxygen carbonyl group via an intramolecular hydrogen bond between the former moiety and the oxygen of the latter, as in the **A** TS (Paquette and Hofferberth, 2003). Because the geometry of the **9b-exo-out-H** conformer allows for the formation of such a hydrogen bond, the ring expansion step would be directed towards the unobserved  $\alpha$ -ketol **15**. The **A** TS is likely destabilized by the electron-deficiency of the protonated oxygen of the carbonyl group.

### 3. Conclusions

The present results indicate that captodative alkene **1a** undergoes highly stereoselective thermal and Lewis acid-catalyzed Diels-Alder reactions with cyclohexadiene (**10**) to furnish the corresponding *endo* adduct **11a** as a single isomer in high yields. The reactivity of  $\alpha$ -ketol bicyclo[2.2.1]heptanes **8b** and **9b**, the hydrolyzed products generated from the cyclopentadiene (**7**) adducts *endo* **8a** and *exo* **9a**, respectively, was evaluated under mCPBA-promoted acyloin rearrangement conditions. Such rearrangement was found to be efficient and stereospecific, rendering the ring expansion products *endo*- and *exo*-hydroxy-*exo*-epoxy tricyclo[3.3.1.0<sup>2,4</sup>]nonan-7-ones **15** and **16**, respectively. In the case of  $\alpha$ -ketol bicyclo[2.2.2]octanes **11b** and **12b**, the epoxidation/Baeyer-Villiger cascade process was preferred, leading to the *syn* ketoepoxide **19b** from each of the isomers. Only  $\alpha$ -ketol bicyclo[2.2.2]octane **11b** was able to undergo acyloin rearrangement by silica gel treatment to stereospecifically produce  $\alpha$ -ketol bicyclo[3.2.2]nonane **22a**. The structure of the latter reveals that the rearrangement took place through a pathway opposite to the one followed by  $\alpha$ -ketol bicyclo[2.2.1]heptanes **8b** and **9b**. The rearrangement of these substrates occurred in a five-step cascade transformation to compound **27**, a potential precursor in the synthesis of racemic  $\beta$ -carbaxylase. Quantum calculations may provide further insight into the controlling effects involved in the *endo* and *exo* transition states for the thermal and Lewis acid-catalyzed Diels-Alder reaction between **1a** and cyclohexadiene (**10**), as well as into the effects promoting the stereospecific acyloin rearrangements of

the bicyclic  $\alpha$ -ketols **8b**, **9b**, **11b** and **12b**. Such calculations are in progress and will be reported in due course.

## 4. Experimental section

### 4.1. General methods

Melting points were determined with an Electrothermal capillary melting point apparatus. IR spectra were recorded on a Perkin-Elmer 2000 spectrophotometer. <sup>1</sup>H (300 or 500 MHz) and <sup>13</sup>C (75.4 or 125 MHz) NMR spectra were recorded on Varian Mercury-300 or Varian VNMR System instruments, with TMS as internal standard. Mass spectra (MS) and high resolution mass spectrometry were conducted in electron impact (70 eV) and fast atom bombardment (FAB) modes, on Hewlett-Packard 5971A and Thermo-Finnigan Polaris Q, and Jeol JSM-GCMat-eII and JMS-SX 102 spectrometers. X-Ray crystallographic measurements were collected on a Siemens P4 diffractometer with Mo K $\alpha$  radiation (graphite crystal monochromator,  $\lambda = 0.7107 \text{ \AA}$ ). Microanalyses were performed by a CE-440 Exeter elemental analyzer instrument. Analytical thin-layer chromatography was carried out with E. Merck silica gel 60 F<sub>254</sub>-coated 0.25 plates, visualized by a long- and short-wavelength UV lamp. For all air moisture sensitive reactions, a nitrogen atmosphere and oven-dried glassware were employed. THF was freshly distilled from sodium, and methylene chloride from calcium hydride prior to use. Triethylamine was freshly distilled from NaOH. All other reagents were used without further purification. Compounds **1a**, **8a-b** and **9a-b** were prepared as previously described (Tamariz and Vogel, 1981; Garca de Alba et al., 1996).

### 4.2. (1*R*\*, 2*S*\*, 4*R*\*)-2-Acetylbicyclo[2.2.2]oct-5-en-2-yl 4-nitrobenzoate (**11a**)

#### 4.2.1. (1*R*\*, 2*R*\*, 4*R*\*)-2-Acetylbicyclo[2.2.2]oct-5-en-2-yl 4-nitrobenzoate (**12a**)

**Method A.** Under N<sub>2</sub> atmosphere and vigorous magnetic stirring, a mixture of **1a** (0.050 g, 0.21 mmol), **10** (0.042 g, 0.53 mmol), and hydroquinone (3 mg) in dry C<sub>6</sub>H<sub>6</sub> (3.0 mL)

was placed at room temperature in a threaded ACE glass pressure tube with a sealed Teflon screw cap and kept in the dark. The mixture was heated to 130 °C for 168 h, then diluted with EtOAc (60 mL), and washed with H<sub>2</sub>O (3 × 15 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (3 g, hexane/EtOAc, 9:1) to give **11a** (0.047 g, 70%) as a pale yellow solid.

**Method B.** Under N<sub>2</sub> atmosphere and vigorous magnetic stirring, to a solution of **1a** (0.050 g, 0.21 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL), BF<sub>3</sub>·Et<sub>2</sub>O (0.567 g, 3.99 mmol) and **10** (0.042 g, 0.53 mmol) were added dropwise at –50 °C. The mixture was stirred at the same temperature for 10 h, then diluted with EtOAc (60 mL) and successively washed with H<sub>2</sub>O (2 × 10 mL), a cold aqueous saturated solution of NaHCO<sub>3</sub> (3 × 15 mL), and a cold saturated solution of NaCl until neutral. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (3 g, hexane/EtOAc, 9:1) to give a mixture of **11a/12a** (67:33) (0.057 g, 85%) as a pale yellow solid.

**Method C.** Following **Method B**, with TiCl<sub>4</sub> (0.345 g, 1.80 mmol) instead BF<sub>3</sub>·Et<sub>2</sub>O, and stirring the mixture for 3 h, a mixture of **11a/12a** (44:56) (0.061 g, 92%) was provided as a pale yellow solid.

**Method D.** Following **Method B**, with AlCl<sub>3</sub> (0.066 g, 0.50 mmol) instead BF<sub>3</sub>·Et<sub>2</sub>O, and stirring the mixture at 0 °C for 1 h, **11a** (0.063 g, 95%) was furnished as a pale yellow solid.

**Method E.** Following **Method B**, with ZnI<sub>2</sub> (1.595 g, 5.00 mmol) instead BF<sub>3</sub>·Et<sub>2</sub>O, and stirring the mixture at 25 °C for 120 h, **11a** (0.056 g, 84%) was produced as a pale yellow solid.

**Data of 11a.** *R*<sub>f</sub> 0.43 (hexane/EtOAc, 8:2); mp 149–150 °C. IR (film) 1722, 1522, 1348, 1279, 1105 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.30 (dddd, *J* = 12.6, 12.2, 4.9, 2.8 Hz, 1H, H-7s'), 1.39 (tdd, *J* = 12.2, 6.3, 3.2 Hz, 1H, H-8s'), 1.59 (dd, *J* = 14.3, 2.4 Hz, 1H, H-3x'), 1.62–1.68 (m, 1H, H-8a'), 2.12–2.19 (m, 1H, H-7a'), 2.14 (s, 3H, CH<sub>3</sub>CO), 2.48 (dt, *J* = 14.3, 3.0 Hz, 1H, H-3n'), 2.77–2.80 (m, 1H, H-4'), 3.10–3.12 (m, 1H, H-1'), 6.14 (td, *J* = 6.9, 1.2 Hz, 1H, H-6'), 6.39 (d, *J* = 7.7, 6.9 Hz, 1H, H-5'), 8.22–8.25 (m, 2H, ArH-2), 8.32–8.34 (m, 2H, ArH-3). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  20.1 (C-7'), 23.7 (C-8'), 24.7 (CH<sub>3</sub>CO), 30.0 (C-4'), 36.2 (C-1'), 36.3 (C-3'), 89.2 (C-2'), 123.7 (Ar-3), 129.5 (C-6'), 130.9 (Ar-2), 135.0 (Ar-1), 135.9 (C-5'), 150.8 (ArC-4), 164.2 (ArCO<sub>2</sub>), 203.7 (CH<sub>3</sub>CO). MS (70 eV) *m/z* (%) 314 (M<sup>+</sup>–1, 2), 272 (36), 150 (100), 120 (4), 104 (12), 76 (5). Anal. Calcd for C<sub>17</sub>H<sub>17</sub>NO<sub>5</sub>: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.96; H, 5.55; N, 4.31.

**Data of 12a.** *R*<sub>f</sub> 0.64 (hexane/EtOAc, 8:2); mp 137–138 °C. IR (KBr) 1716, 1524, 1353, 1299, 1107, 722 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.17–1.28 (m, 2H, H-7s', H-8'), 1.33 (dt, *J* = 14.1, 2.4 Hz, 1H, H-3n'), 1.38–1.47 (m, 1H, H-7a'), 1.55–1.62 (m, 1H, H-8a'), 2.16 (s, 3H, CH<sub>3</sub>CO), 2.73 (br s, 1H, H-4'), 2.90 (dd, *J* = 14.1, 2.4 Hz, 1H, H-3x'), 2.94 (br s, 1H, H-1'), 6.37–6.50 (m, 2H, H-5', H-6'), 8.14–8.20 (m, 2H, ArH-2), 8.27–8.33 (m, 2H, ArH-3). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>)  $\delta$  19.8 (C-7'), 21.9 (C-8'), 23.9 (CH<sub>3</sub>CO), 30.1 (C-4'), 36.0 (C-1'), 37.2 (C-3'), 91.4 (C-2'), 123.6 (Ar-3), 130.0 (C-5'), 130.9 (Ar-2), 135.0 (Ar-1), 136.1 (C-6'), 150.7 (Ar-4), 163.9 (ArCO<sub>2</sub>), 204.3 (CH<sub>3</sub>CO). MS (70 eV) *m/z* (%) 150

(M<sup>+</sup>–164, 100), 134 (3), 120 (6), 104 (28), 92 (14), 76 (21). HRMS (EI) calcd for [M + 1]<sup>+</sup> C<sub>17</sub>H<sub>18</sub>NO<sub>5</sub>: 316.1185. Found: 316.1179.

#### 4.3. 1-((1*R*\*, 2*S*\*, 4*R*\*)-2-Hydroxybicyclo[2.2.2]oct-5-en-2-yl) ethanone (**11b**)

Under N<sub>2</sub> atmosphere and vigorous magnetic stirring, to a solution of **11a** (0.400 g, 1.27 mmol) in anhydrous THF (7.0 mL), K<sub>2</sub>CO<sub>3</sub> (0.910 g, 6.60 mmol) in anhydrous MeOH (2.0 mL) was added dropwise at 25 °C. The mixture was stirred at the same temperature for 4 h, then diluted with EtOAc (60 mL) and successively washed with H<sub>2</sub>O until neutral. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (15 g, hexane/EtOAc, 8:2) to obtain **11b** (0.198 g, 94%) as a pale yellow oil. *R*<sub>f</sub> 0.35 (hexane/EtOAc, 8:2). IR (film) 3455, 2942, 1703, 1354, 1101 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.09 (tdd, *J* = 12.1, 5.4, 2.6 Hz, 1H, H-7s), 1.31 (tdd, *J* = 12.1, 6.5, 3.2 Hz, 1H, H-8s), 1.47 (dd, *J* = 13.6, 2.6 Hz, 1H, H-3x), 1.67–1.78 (m, 1H, H-8a), 1.92 (dt, *J* = 13.6, 2.9 Hz, 1H, H-3n), 2.19 (s, 3H, CH<sub>3</sub>CO), 2.19–2.30 (m, 1H, H-7a), 2.43–2.47 (m, 1H, H-1), 2.73–2.77 (m, 1H, H-4), 3.81 (br s, 1H, OH), 6.23–6.40 (m, 2H, H-5, H-6). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>)  $\delta$  20.6 (C-7), 23.4 (C-8), 25.6 (CH<sub>3</sub>CO), 30.4 (C-4), 38.9 (C-1), 39.0 (C-3), 80.5 (C-2), 132.7 (C-6), 134.6 (C-5), 211.3 (CH<sub>3</sub>CO). MS (70 eV) *m/z* (%) 166 (M<sup>+</sup>, 1), 123 (10), 105 (2), 95 (100), 94 (13), 80 (54), 79 (50), 77 (52), 67 (11). Anal. Calcd for C<sub>10</sub>H<sub>14</sub>O<sub>2</sub>: C, 72.26; H, 8.49. Found: C, 72.40; H, 8.47.

#### 4.4. 1-((1*R*\*, 2*R*\*, 4*R*\*)-2-Hydroxybicyclo[2.2.2]oct-5-en-2-yl) ethanone (**12b**)

According to the procedure used for the preparation of **11b**, with **12a** (0.134 g, 0.426 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.292 g, 2.12 mmol) in anhydrous MeOH (2.0 mL) and stirring for 4 h, **12b** (0.057 g, 81%) was delivered as a pale yellow oil. *R*<sub>f</sub> 0.34 (hexane/EtOAc, 8:2). IR (film) 3460, 2944, 1711, 1351, 1110, 722 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.04–1.25 (m, 3H, H-3n, H-7, H-8), 1.36–1.54 (m, 2H, H-7, H-8), 2.11 (br s, 1H, OH), 2.30 (s, 3H, CH<sub>3</sub>CO), 2.47 (dd, *J* = 13.8, 2.1 Hz, 1H, H-3x), 2.68–2.78 (m, 2H, H-1, H-4), 6.24 (ddd, *J* = 8.1, 6.6, 1.5 Hz, 1H, H-6), 6.54 (ddd, *J* = 7.8, 6.6, 1.2 Hz, 1H, H-5). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>)  $\delta$  19.9 (C-7), 23.0 (C-8), 25.0 (CH<sub>3</sub>CO), 30.4 (C-4), 39.2 (C-1), 39.7 (C-3), 82.9 (C-2), 129.8 (C-6), 138.1 (C-5), 210.3 (CH<sub>3</sub>CO). MS (70 eV) *m/z* (%) 167 (M<sup>+</sup> + 1, 100), 149 (54), 145 (34), 133 (40), 123 (50), 111 (46), 97 (56), 95 (82), 81 (54), 79 (38), 67 (31). Anal. Calcd for C<sub>10</sub>H<sub>14</sub>O<sub>2</sub>: C, 72.26; H, 8.49. Found: C, 72.24; H, 8.51.

#### 4.5. (1*R*\*, 2*R*\*, 4*S*\*, 5*R*\*, 6*S*\*)-6-Hydroxy-6-methyl-3-oxatricyclo[3.3.1.0<sup>2,4</sup>]nonan-7-one (**15**)

Under N<sub>2</sub> atmosphere and vigorous magnetic stirring, to a solution of **8b** (0.100 g, 0.66 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (3 mL), mCPBA (0.112 g, 0.65 mmol) and Na<sub>2</sub>SO<sub>4</sub> (0.5 g) were added at room temperature. The mixture was stirred at the same temperature for 24 h and then diluted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The organic solution was successively washed with H<sub>2</sub>O

(2 × 10 mL), an aqueous saturated solution of NaHCO<sub>3</sub> (3 × 10 mL) and brine until neutral. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent evaporated under vacuum. The residue was purified by column chromatography over silica gel (10 g, hexane/EtOAc, 7:3) to give **15** (0.075 g, 68%) as a white solid. *R<sub>f</sub>* 0.54 (hexane/EtOAc, 7:3); mp 142–143 °C. IR (CH<sub>2</sub>Cl<sub>2</sub>) 3468, 2930, 1708, 1452, 1368, 1142, 1084, 1010, 984, 838 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.35 (s, 3H, CH<sub>3</sub>), 1.59 (br d, *J* = 12.9 Hz, 1H, H-9a), 1.67–1.77 (m, 1H, H-9s), 2.49 (ddd, *J* = 17.3, 3.3, 3.0 Hz, 1H, H-8 α), 2.59–2.67 (m, 3H, H-1, H-5, H-8β), 3.27 (br d, *J* = 3.0 Hz, 1H, H-2), 3.56 (s, 1H, HO), 3.61 (br d, *J* = 3.0 Hz, 1H, H-4). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>) δ 25.4 (C-9), 26.0 (CH<sub>3</sub>), 34.8 (C-1), 41.4 (C-8), 44.9 (C-5), 52.9 (C-4), 54.0 (C-2), 78.8 (C-6), 213.5 (CO); MS (70 eV) *m/z* (%) 168 (M<sup>+</sup>, 9), 140 (5), 111 (55), 97 (51), 82 (57), 69 (27), 55 (25), 43 (100). Anal. Calcd for C<sub>9</sub>H<sub>12</sub>O<sub>3</sub>: C, 64.27; H, 7.19. Found: C, 64.45; H, 7.30.

4.6. (1*R*\*, 2*R*\*, 4*S*\*, 5*R*\*, 6*R*\*)-6-Hydroxy-6-methyl-3-oxatricyclo[3.3.1.0<sup>2,4</sup>]nonan-7-one (**16**)

According to the procedure used for the preparation of **15**, with **9b** (0.300 g, 1.97 mmol) and mCPBA (0.339 g, 1.97 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (7 mL) and Na<sub>2</sub>SO<sub>4</sub> (0.5 g) **16** (0.215, 65%) was afforded as a white solid. *R<sub>f</sub>* 0.56 (hexane/EtOAc, 7:3); mp 139–140 °C. IR (film) 3564, 2972, 1708, 1278, 1256 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.36 (s, 3H, CH<sub>3</sub>), 1.46–1.56 (m, 1H, H-9s), 1.88–1.96 (m, 1H, H-9a), 2.32 (dm, *J* = 18.0 Hz, 1H, H-8α), 2.53–2.60 (m, 2H, H-1, H-5), 2.75 (dm, *J* = 18.0 Hz, 1H, H-8β), 3.28 (dm, *J* = 3.9 Hz, 1H, H-4), 3.35 (dm, *J* = 3.9 Hz, 1H, H-2). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>) δ 22.3 (CH<sub>3</sub>), 22.8 (C-9), 33.5 (C-1), 40.9 (C-8), 44.9 (C-5), 51.9 (C-4), 55.1 (C-2), 75.8 (C-6), 209.9 (CO). MS (70 eV) *m/z* (%) 168 (M<sup>+</sup>, 16), 140 (6), 111 (52), 97 (53), 82 (51), 81 (52), 69 (27), 43 (100). Anal. Calcd for C<sub>9</sub>H<sub>12</sub>O<sub>3</sub>: C, 64.27; H, 7.19. Found: C, 64.39; H, 6.95.

4.7. (1*R*\*, 2*R*\*, 4*S*\*, 5*R*\*)-3-Oxatricyclo[3.2.2.0<sup>2,4</sup>]nonan-6-one (**19b**)

**Method A:** Under N<sub>2</sub> atmosphere and vigorous magnetic stirring, a mixture of **11b** (0.090 g, 0.54 mmol) and mCPBA (0.465 g, 2.70 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL) was stirred at 20 °C for 24 h. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (60 mL) and washed with H<sub>2</sub>O (2 × 10 mL), an aqueous saturated solution of NaHCO<sub>3</sub> (3 × 10 mL) and with brine until neutral. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent evaporated under vacuum. The residue was purified by column chromatography over silica gel (15 g, hexane/EtOAc, 7:3) to afford **19b** (0.047 g, 64%) as a white solid.

**Method B:** According to **Method A**, with **12b** (0.050 g, 0.30 mmol) and mCPBA (0.258 g, 1.50 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (3 mL), **19b** (0.025 g, 61%) was furnished as a white solid. *R<sub>f</sub>* 0.25 (hexane/EtOAc, 7:3); mp 147–148 °C. IR (film) 2927, 1727, 1467, 1377, 1275, 1126, 1073 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.62–1.82 (m, 3H, H-8, H-9), 1.84–1.92 (m, 1H, H-8), 1.96 (dd, *J* = 18.7, 2.7 Hz, 1H, H-7α), 2.29 (dm, *J* = 18.7 Hz, 1H, H-7β), 2.58–2.68 (m, 1H, H-1), 2.83–2.90 (m, 1H, H-5), 3.44–3.54 (m, 2H, H-2, H-4). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>) δ 19.6 (C-9), 21.4 (C-8), 28.3 (C-1), 40.5 (C-7), 44.8 (C-5), 49.2 (C-4), 51.9 (C-2), 209.7 (CO). Anal.

Calcd for C<sub>8</sub>H<sub>10</sub>O<sub>2</sub>: C, 69.54; H, 7.30. Found: C, 69.53; H, 7.32.

4.8. (1*R*\*, 2*R*\*, 5*R*\*)-2-Hydroxy-2-methylbicyclo[3.2.2]non-6-en-3-one (**22a**)

A solution of **11b** (0.400 g, 1.27 mmol) in a mixture of dry hexane/EtOAc (7:3) (2 mL) was poured into a chromatography column over silica gel (5 g, hexane/EtOAc, 7:3) and maintained at room temperature for 120 h. The column was eluted (hexane/EtOAc, 7:3), resulting in **22a** (0.125 g, 59%) as a pale yellow oil. *R<sub>f</sub>* 0.85 (hexane/EtOAc, 7:3). IR (film) 3431, 2950, 1639 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.26 (s, 3H, CH<sub>3</sub>), 1.43–1.73 (m, 3H, H-8, 2H-9), 1.80–1.95 (m, 1H, H-8), 2.50–2.74 (m, 4H, H-1, H-4, H-5), 4.32 (s, 1H, HO), 6.33 (dd, *J* = 9.1, 7.9 Hz, 1H, H-7), 6.42 (dd, *J* = 9.1, 6.3 Hz, 1H, H-6). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>) δ 20.2 (C-8), 23.6 (C-9), 26.3 (CH<sub>3</sub>), 29.3 (C-5), 41.2 (C-1), 45.6 (C-4), 81.4 (C-2), 132.7 (C-7), 135.6 (C-6), 215.1 (CO). MS (70 eV) *m/z* (%) 166 (M<sup>+</sup>, 2), 123 (21), 105 (5), 95 (100), 80 (90), 79 (60), 77 (41), 67 (13), 65 (11). HRMS (EI) *m/z* [M<sup>+</sup>] calcd for C<sub>10</sub>H<sub>14</sub>O<sub>2</sub>: 166.0994. Found: 166.0991.

4.9. (1*R*\*, 2*R*\*, 5*R*\*)-2-Methyl-3-oxobicyclo[3.2.2]non-6-en-2-yl 4-nitrobenzoate (**23**)

Under N<sub>2</sub> atmosphere and vigorous magnetic stirring, to a solution of **22a** (0.022 g, 0.13 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (8 mL), triethylamine (0.013 g, 0.13 mmol), DMAP (0.016 g, 0.13 mmol) and *p*-nitrobenzoyl chloride (0.024 g, 0.13 mmol) were added dropwise at room temperature. The mixture was stirred at the same temperature for 6 h, then diluted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and washed with a cold 5% aqueous solution of HCl (2 × 20 mL) and brine until neutral. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (30 g, hexane/EtOAc, 95:5) to produce **23** (0.039 g, 94%) as a pale yellow solid. *R<sub>f</sub>* 0.49 (hexane/EtOAc, 8:2); mp 99–101 °C. IR (KBr) 1719, 1524, 1350, 1289, 1103, 716 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.54–1.72 (m, 2H, H-8s', H-9s'), 1.76 (s, 3H, CH<sub>3</sub>), 1.78–1.92 (m, 1H, H-9a'), 1.98–2.09 (m, 1H, H-8a'), 2.60–2.84 (m, 3H, H-4', H-5'), 3.08–3.16 (m, 1H, H-1'), 6.30 (t, *J* = 8.4 Hz, 1H, H-7'), 6.50 (dd, *J* = 8.4, 6.3 Hz, 1H, H-6'), 8.17–8.26 (m, 2H, H-2), 8.26–8.35 (m, 2H, H-3). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>) δ 21.2 (C-8'), 22.8 (CH<sub>3</sub>), 24.3 (C-9'), 29.3 (C-5'), 40.2 (C-1'), 47.4 (C-4'), 90.5 (C-2'), 123.5 (C-3), 130.7 (C-7'), 130.8 (C-2), 136.3 (C-1), 137.1 (C-6'), 150.4 (C-4), 163.4 (ArCO<sub>2</sub>), 206.0 (CO). HRMS (EI) *m/z* [M<sup>+</sup>] calcd for C<sub>17</sub>H<sub>17</sub>NO<sub>5</sub>: 315.1107. Found: 315.1119.

4.10. (3*aR*\*, 5*R*\*, 6*S*\*, 6*aS*\*)-5-Acetyl-6-hydroxyhexahydro-2*H*-cyclopenta[*b*]furan-2-one (**26**)

Following the method for the preparation of **15**, **9b** (0.20 g, 1.3 mmol), mCPBA (0.448 g, 2.60 mmol) and Na<sub>2</sub>SO<sub>4</sub> (0.5 g) were used in dry CH<sub>2</sub>Cl<sub>2</sub> (3 mL). The crude of the reaction was purified by column chromatography over silica gel (6.0 g, hexane/EtOAc, 6:4), obtaining **26** (0.109 g, 45%) as a pale yellow oil. Following this method, with a mixture of **8a/9b** (0.20 g, 1.3 mmol), mCPBA (0.448 g, 2.60 mmol) and

Na<sub>2</sub>SO<sub>4</sub> (0.5 g) in dry CH<sub>2</sub>Cl<sub>2</sub> (3 mL), **26** (0.17 g, 70%) was delivered as a pale yellow oil. *R<sub>f</sub>* 0.18 (hexane/EtOAc, 7:3). IR (CH<sub>2</sub>Cl<sub>2</sub>) 3417, 1771, 1705, 1362, 1170, 1034 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.68–1.80 (m, 1H, H-4 $\beta$ ), 2.25 (s, 3H, CH<sub>3</sub>CO), 2.27–2.38 (m, 1H, H-4 $\alpha$ ), 2.39 (dd, *J* = 18.4, 2.9 Hz, 1H, H-3 $\beta$ ), 2.77 (dd, *J* = 18.4, 9.9 Hz, 1H, H-3 $\alpha$ ), 2.95–3.11 (m, 2H, H-3a, H-5), 3.58 (br s, 1H, OH), 4.43 (dd, *J* = 8.0, 3.3 Hz, 1H, H-6), 4.76 (dd, *J* = 8.0, 3.3 Hz, 1H, H-6a). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>)  $\delta$  29.7 (CH<sub>3</sub>CO), 32.4 (C-4), 35.1 (C-3), 35.5 (C-3a), 58.2 (C-5), 79.0 (C-6), 80.3 (C-6a), 176.8 (C-2), 207.9 (CH<sub>3</sub>CO). MS (70 eV) *m/z* (%) 166 (M<sup>+</sup>–18, 4), 151 (7), 123 (9), 121 (15), 107 (61), 79 (100), 77 (66). HRMS (EI) *m/z* [M<sup>+</sup>] calcd for C<sub>9</sub>H<sub>12</sub>O<sub>4</sub>: 184.0736. Found: 184.0742.

4.11. (3aR\*, 5R\*, 6S\*, 6aS\*)-6-Hydroxy-2-oxohexahydro-2H-cyclopenta[b]furan-5-yl acetate (**27**)

A mixture of **8b/9b** (30:70) (0.40 g, 2.63 mmol), mCPBA (1.360 g, 7.88 mmol) and Na<sub>2</sub>SO<sub>4</sub> (1.0 g) in a dry mixture of heptane/CH<sub>2</sub>Cl<sub>2</sub> (8:2, 50 mL) was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap and kept in the dark. The mixture was stirred at room temperature for 2 weeks and the solvent was removed under vacuum. The crude of the reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and filtered, followed by removal of the solvent under vacuum. The crude was purified by column chromatography over silica gel (90 g, hexane/EtOAc, 7:3), leading to **27** (0.294 g, 56%) as a white solid. *R<sub>f</sub>* 0.45 (EtOAc); mp 99–101 °C. IR (CH<sub>2</sub>Cl<sub>2</sub>) 3433, 1771, 1735, 1373, 1239, 1170, 1051 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.81 (ddd, *J* = 14.2, 3.5, 3.3 Hz, 1H, H-4 $\alpha$ ), 2.05 (s, 3H, CH<sub>3</sub>CO<sub>2</sub>), 2.43 (dd, *J* = 18.3, 3.0 Hz, 1H, H-3 $\alpha$ ), 2.51 (ddd, *J* = 14.4, 8.7, 5.1 Hz, 1H, H-4 $\beta$ ), 2.88 (dd, *J* = 18.3, 11.0 Hz, 1H, H-3 $\beta$ ), 3.13–3.25 (m, 1H, H-3a), 3.40–3.72 (br, 1H, OH), 4.31 (br s, 1H, H-6), 4.82 (d, *J* = 7.5 Hz, 1H, H-6a), 4.95–5.02 (m, 1H, H-5). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>)  $\delta$  20.9 (CH<sub>3</sub>CO<sub>2</sub>), 35.1 (C-3a), 35.9 (C-3), 36.4 (C-4), 78.4 (C-6), 80.1 (C-5), 88.7 (C-6a), 171.1 (CH<sub>3</sub>CO<sub>2</sub>), 177.2 (C-2). MS (70 eV) *m/z* (%) 201 (M<sup>+</sup>+1, 1), 182 (2), 140 (65), 112 (22), 97 (31), 84 (36), 43 (100). Anal. Calcd for C<sub>9</sub>H<sub>12</sub>O<sub>5</sub>: C, 53.99; H, 6.04. Found: C, 53.83; H, 5.87.

4.12. (3aR\*, 6aS\*)-5-Acetyl-3,3a,4,6a-tetrahydro-2H-cyclopenta[b]furan-2-one (**28**)

Under N<sub>2</sub> atmosphere and vigorous magnetic stirring, to a solution of **26** (0.150 g, 0.85 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (1 mL), DBU (0.487 g, 3.20 mmol) and SOCl<sub>2</sub> (0.19 g, 1.6 mmol) were added dropwise at 0 °C. At the same temperature, the mixture was stirred for 20 min and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (10 g, hexane/EtOAc, 9:1), rendering **28** (0.103 g, 76%) as a pale yellow oil. *R<sub>f</sub>* 0.85 (hexane/EtOAc, 7:3). IR (CH<sub>2</sub>Cl<sub>2</sub>) 1768, 1673, 1372, 1337, 1288, 1250, 1203, 1163, 1054, 1011, 904 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  2.34 (dd, *J* = 18.5, 6.2 Hz, 1H, H-3), 2.40 (s, 3H, CH<sub>3</sub>CO), 2.54 (ddd, *J* = 17.5, 4.4, 2.3 Hz, 1H, H-4), 2.88 (dd, *J* = 18.5, 10.7 Hz, 1H, H-3), 2.86–2.97 (m, 1H, H-4), 3.21–3.33 (m, 1H, H-3a), 5.67 (dm, *J* = 7.7 Hz, 1H, H-6a), 6.60–6.64 (m, 1H, H-6). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>)  $\delta$  26.9 (CH<sub>3</sub>CO), 35.0 (C-3a), 35.4 (C-3 or C-4), 37.2 (C-4 or C-3), 88.7 (C-6a),

136.8 (C-6), 148.0 (C-5), 176.4 (C-2), 196.6 (CH<sub>3</sub>CO). MS (70 eV) *m/z* (%) 166 (M<sup>+</sup>, 37), 151 (31), 123 (18), 121 (34), 107 (91), 95 (30), 79 (88), 77 (65), 67 (31), 43 (100). HRMS (FAB) (mNBA) (MH)<sup>+</sup> *m/z* calculated for C<sub>9</sub>H<sub>11</sub>O<sub>3</sub>: 167.0708; found: 167.0710.

4.13. (2R\*, 3aR\*, 5R\*, 6S\*, 6aS\*)-2,6-Dihydroxyhexahydro-2H-cyclopenta[b]furan-5-yl acetate (**29a**). (2S\*, 3aR\*, 5R\*, 6S\*, 6aS\*)-2,6-Dihydroxyhexahydro-2H-cyclopenta[b]furan-5-yl acetate (**29b**)

To a solution of **27** (0.050 g, 0.25 mmol) in anhydrous THF (1 mL), under N<sub>2</sub> atmosphere and vigorous magnetic stirring, a 1.0 M of DIBAL in THF (0.5 mL, 0.5 mmol) was added at –78 °C. The mixture was stirred at the same temperature for 15 min, and a suspension of 5% of NH<sub>4</sub>Cl in MeOH (5 mL) was added. While the mixture was stirred for 2 h, the temperature rose to room temperature. The mixture was filtered and the solvent removed under vacuum. The crude was purified by column chromatography over silica gel (5 g, hexane/EtOAc, 7:3), generating a mixture of **29a/29b** (59:41) (0.023, 45%) as a pale yellow oil. *R<sub>f</sub>* 0.30 (EtOAc). IR (CH<sub>2</sub>Cl<sub>2</sub>) 3392, 1730, 1442, 1373, 1241, 1068, 1031 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  signals attributed to the major isomer: 1.52–1.65 (m, 1H, H-4), 1.84–2.05 (m, 1H, H-3), 2.07 (s, 3H, CH<sub>3</sub>CO<sub>2</sub>), 2.32–2.39 (m, 1H, H-4), 2.90–3.06 (m, 1H, H-3a), 3.64–3.82 (m, 1H, HO), 4.10 (dd, *J* = 5.1, 2.4 Hz, 1H, H-6), 4.52 (dd, *J* = 7.8, 2.4 Hz, 1H, H-6a), 4.79–4.87 (m, 1H, H-5), 5.62–5.66 (m, 1H, H-2); signals attributed to the minor isomer: 2.05–2.18 (m, 2H, H-3, H-4), 2.09 (s, 3H, CH<sub>3</sub>CO<sub>2</sub>), 2.39–2.46 (m, 1H, H-4), 2.69–2.82 (m, 1H, H-3a), 3.82–4.00 (m, 1H, HO), 4.34 (dd, *J* = 7.5, 4.2 Hz, 1H, H-6), 4.40 (dd, *J* = 8.7, 4.2 Hz, 1H, H-6a), 4.87–4.96 (m, 1H, H-5), 5.66–5.70 (m, 1H, H-2). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>)  $\delta$  signals attributed to the major isomer: 21.1 (CH<sub>3</sub>CO<sub>2</sub>), 35.5 (C-4), 37.4 (C-3a), 40.7 (C-3), 80.6 (C-6), 81.7 (C-5), 88.0 (C-6a), 100.1 (C-2), 171.7 (CH<sub>3</sub>CO<sub>2</sub>); signals attributed to the minor isomer: 34.6 (C-4), 36.3 (C-3a), 39.2 (C-3), 80.0 (C-5), 82.6 (C-6), 89.4 (C-6a), 100.9 (C-2), 172.1 (CH<sub>3</sub>CO<sub>2</sub>); MS (70 eV) *m/z* (%) 185 (M<sup>+</sup>–17, 6), 184 (M<sup>+</sup>–18, 6), 142 (12), 124 (50), 96 (34), 95 (100), 82 (42), 81 (74), 67 (47). HRMS (FAB) (mNBA) *m/z* [MH]<sup>+</sup> calculated for C<sub>9</sub>H<sub>15</sub>O<sub>5</sub>: 203.0919; found: 203.0918.

4.14. Single-crystal X-Ray crystallography

Compounds **11a** and **12a** were obtained as pale yellow crystals, and compound **16** as colorless crystals. These were mounted on glass fibers. Crystallographic measurements were carried out at room temperature in a Siemens P4 diffractometer equipped with a graphite monochromator, with Mo K $\alpha$  radiation ( $\lambda$  = 0.7107 Å) for **11a** and **16**, and Cu K $\alpha$  radiation ( $\lambda$  = 1.5418 Å) for **12a**. In all cases, three standard reflections were monitored periodically and they showed no change during data collection. Unit cell parameters were obtained from least-squares refinement of 28 reflections in the range 4.63 <  $\theta$  < 12.18° for **11a**, 39 reflections in the range 11.87 <  $\theta$  < 28.15° for **12a**; and 41 reflections in the range 5.36 <  $\theta$  < 15.58° for **16**. Intensities were corrected for Lorentz and polarization effects. Although no absorption corrections were made to the diffraction data of **11a**, empirical

corrections (psi-scans) were applied to the data of **12a** and **16**. Anisotropic temperature factors were introduced for all non-hydrogen atoms. Hydrogen atoms were placed in idealized positions and their atomic coordinates refined by using unit weights. The structure was solved and refined with the SHELX-97 program package (Shedrick, 2008) running under the WinGX environment (Farrugia, 1999, 2012) and visualized and plotted with the Ortep-3 program (Farrugia, 1997, 2012). Data on **11a**: (CCDC 1499434) Formula: C<sub>17</sub>H<sub>17</sub>NO<sub>5</sub>; molecular weight: 315.32; cryst. syst.: monoclinic; space group: P2<sub>1</sub>/c; unit cell parameters: *a*, 8.3876(19), *b*, 17.584(3), *c*, 11.1855(15) (Å); α, 90, β, 108.93(2), γ, 90 (deg); *V* = 1560.5 (5) Å<sup>3</sup>; temp. (K): 293(2); *Z*: 4; no. of reflections collected: 4365; no. of independent reflections: 3402; no. of reflections observed: 1662; data collection range: 2.25 < θ < 27.00°; *R*: 0.0697; *wR*: 0.1781; GOF: 1.010. Data on **12a**: (CCDC 1499435) Formula: C<sub>17</sub>H<sub>17</sub>NO<sub>5</sub>; molecular weight: 315.32; cryst. syst.: monoclinic; space group: P2<sub>1</sub>/n; unit cell parameters: *a*, 7.2332(12), *b*, 20.794(4), *c*, 10.7106(17) (Å); α, 90, β, 101.31(2), γ, 90 (deg); *V* = 1579.7(5) Å<sup>3</sup>; temp. (K): 293(2); *Z*: 4; no. of reflections collected: 2887; no. of independent reflections: 2124; no. of reflections observed: 1737; data collection range: 4.25 < θ < 56.93°; *R*: 0.0705; *wR*: 0.0836; GOF: 1.013. Data on **16**: (CCDC 1499436) Formula: C<sub>9</sub>H<sub>12</sub>O<sub>2</sub>; molecular weight: 168.19; cryst. syst.: monoclinic; space group: P2<sub>1</sub>/n; unit cell parameters: *a*, 6.8247(5), *b*, 9.7191(11), *c*, 12.2271(12) (Å); α, 90, β, 91.237(8), γ, 90 (deg); *V* = 810.83 (14) Å<sup>3</sup>; temp. (K): 293(2); *Z*: 4; no. of reflections collected: 2818; no. of independent reflections: 2044; no. of reflections observed: 1591; data collection range: 2.68 < θ < 28.49°; *R*: 0.0486; *wR*: 0.1227; GOF: 1.043. The authors have deposited the atomic coordinates for these structures with the Cambridge Crystallographic Data Center (CCDC 1499434, 1499435, and 1499436). The coordinates can be obtained, on request, from the director of the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.

### Acknowledgments

We thank Fabiola Jiménez for her help in spectrometric measurements and Bruce A. Larsen for proofreading. J.T. would like to acknowledge the financial support provided by the Secretaría de Investigación y Posgrado (SIP)-IPN (Grants 20130686, 20140858, 20150917, 20160791, and 20170902) and CONACYT (Grants 83446 and 178319). M.A.V. thanks Dirección de Apoyo a la Investigación y al Posgrado (DAIPUG) (Grant 811/2016). R.M.P. is grateful to CONACYT for a postdoctoral fellowship. R.A., B.M.S., and D.Z.-Z. are beholden to CONACYT for graduate fellowships, to the Programa Institucional de Formación de Investigadores (PIFI)-IPN program, and to the Ludwig K. Hellweg Foundation for scholarships awarded. J.T. and H.A.J.-V. are fellows of the Estímulos al Desempeño de los Investigadores (EDI)-IPN and Comisión de Operación y Fomento de Actividades Académicas (COFAA)-IPN programs.

### Appendix A. Supplementary material

Supplementary data (<sup>1</sup>H and <sup>13</sup>C NMR spectra of compounds **11a-b**, **12a-b**, **15**, **16**, **19b**, **22a**, **23**, **26-29**, and **31a-b**) associated

with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.arabjc.2017.08.008>.

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