

The intramolecular aldol condensation of 3-oxocyclohexaneacetaldehydes: a useful tool in the synthesis of natural products

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Dedicated to Professor Sándor Antus on his 60th birthday

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Abstract

The intramolecular aldol condensation of 3-oxocyclohexaneacetaldehydes leading to C(6) epimeric mixtures of 6-hydroxybicyclo[2.2.2]octan-2-ones is reviewed. Both steps, the preparation of the 3-oxocyclohexaneacetaldehyde and its cyclization were examined, as well as applications to the synthesis of natural products.

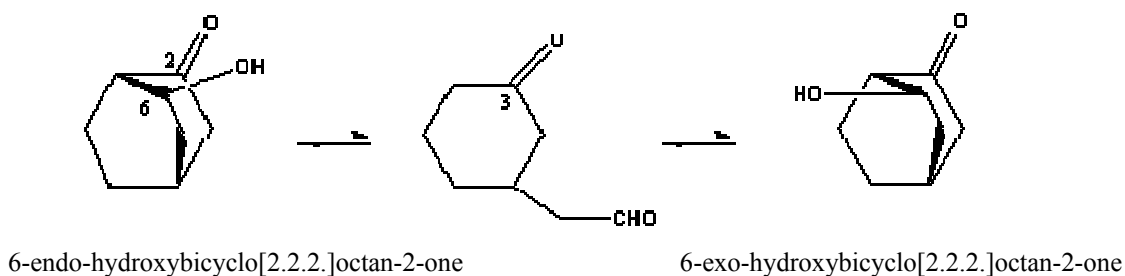
Keywords: 3-Oxocyclohexaneacetaldehydes, preparation, intramolecular aldol condensation

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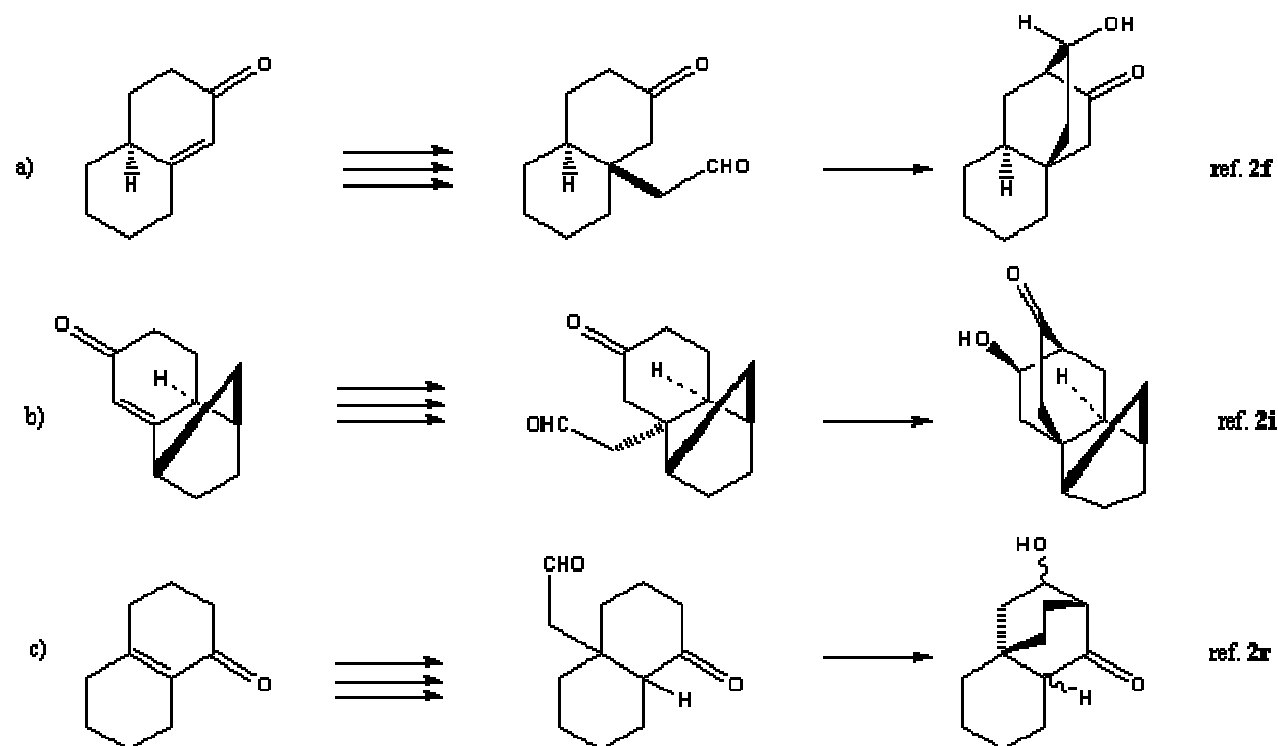
Introduction

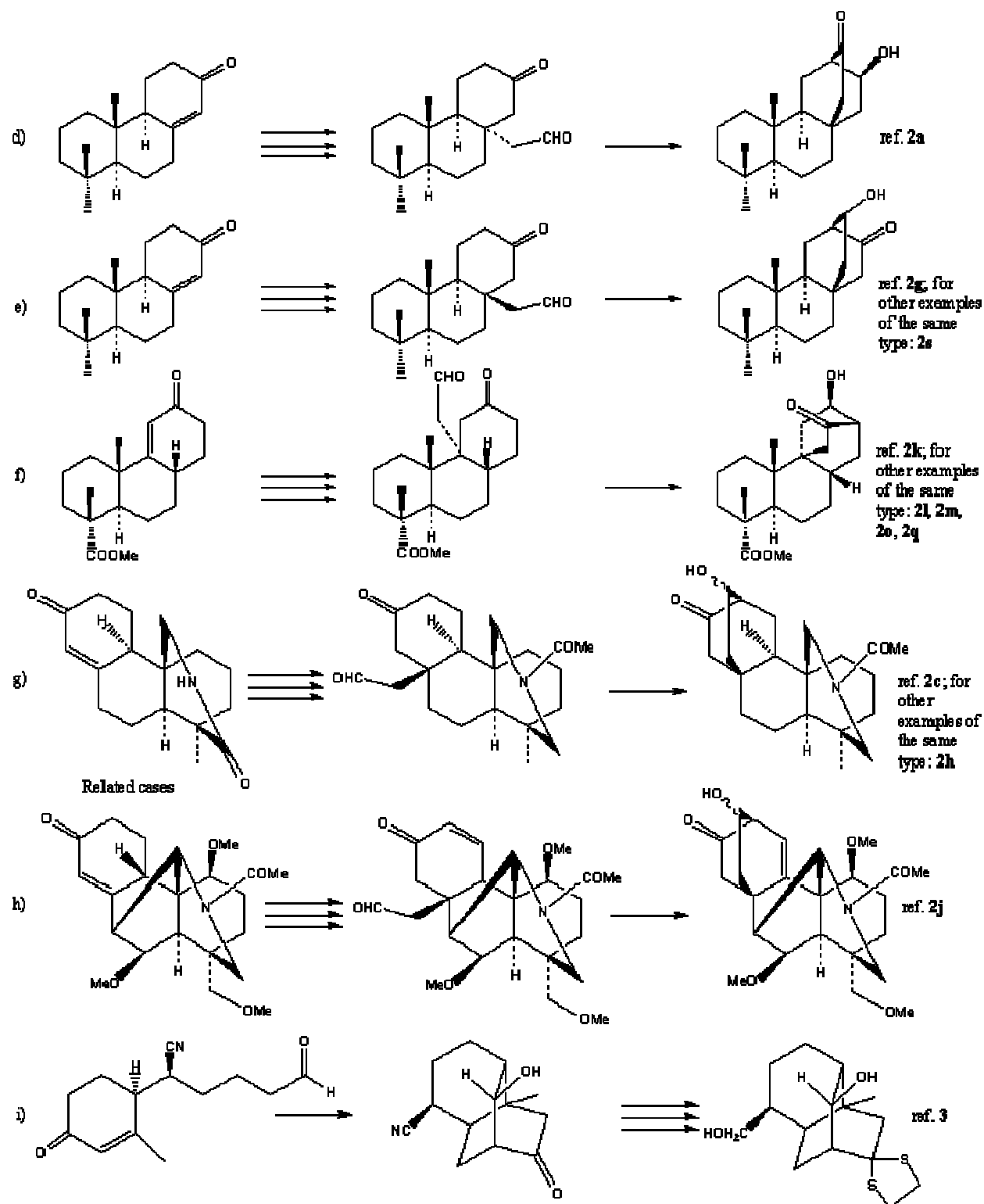
The intramolecular aldol condensation of a 3-oxocyclohexanecarbaldehyde, leading to a C(6) epimeric mixture of 6-hydroxybicyclo[2.2.2]octan-2-ones¹ (Scheme 1), was first described in 1963 by Bell and Ireland in the frame of synthetic studies addressed to the alkaloid atisine.^{2a}



Scheme 1

Since then this reaction was used many times. An array of examples is reported in Scheme 2.





Scheme 2

The importance of this intramolecular process stems from the fact that it leads to a bicyclo[2.2.2]octane system, a moiety present in a number of natural products or intermediates in their synthesis.

Besides, a feature very advantageous in view of further elaboration is that the bicyclo[2.2.2]octane system emerges from the condensation substituted at C(2) and C(6) with oxygenated functions at different oxidation levels [HO-C(6) and O=C(2)].⁴ For reasons which will be explained in the sequel, the HO-C(6) in the major epimer is *endo* oriented.

There are two crucial steps in the process of constructing a 6-hydroxybicyclo[2.2.2]octan-2-one by intramolecular aldol condensation:

- the preparation of the 3-oxocyclohexaneacetaldehyde moiety;
- its cyclization.

1. Preparation of the 3-oxocyclohexaneacetaldehyde moiety

1.1 General remarks

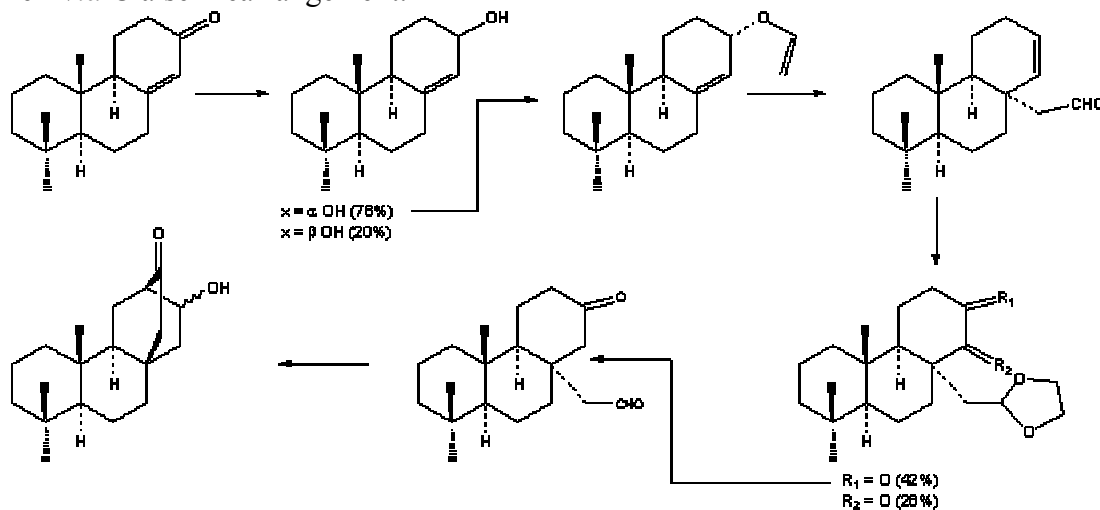
The 3-oxocyclohexaneacetaldehyde moieties were prepared from a 2-cyclohexen-1-one installing at C(3) by various means a formylmethyl side chain.⁵

This step is of crucial importance since, depending on the configuration of the newly created stereogenic center at C(3), diastereomeric products might be obtained. See for instance entries d) and e) in Scheme 2.⁶

1.2 Methodologies adopted

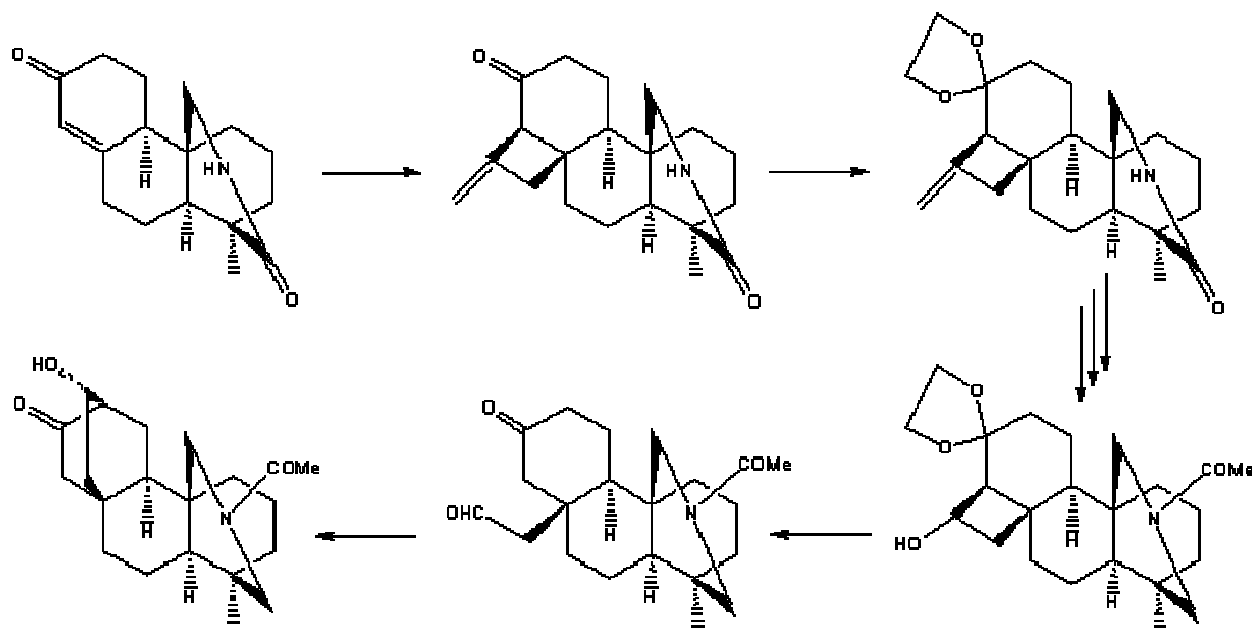
The most adopted methods for the preparation of 3-oxocyclohexaneacetaldehydes from a 2-cyclohexen-1-one are the Claisen rearrangement of the derived vinyl ethers^{2a, 2d} and the allene photoaddition.^{2b-c, 2f-o, 2q-s}

The Claisen rearrangement approach is rather lengthy and suffers the loss of the oxygen function at C(1)⁵ and its not fully regioselective reintroduction. As an example, Scheme 3 shows the preparation of the 3-oxocyclohexaneacetaldehyde key intermediate in the Ireland synthesis of kaurene^{2d} via Claisen rearrangement.



Scheme 3

The allene photoaddition⁷ is a very efficient and clean methodology suitable also for hindered 2-cyclohexen-1-ones. A further advantage of the latter methodology is its high stereoselectivity in the cases described. An example of the allene photoaddition reaction applied to obtaining the 3-oxo-cyclohexaneacetaldehyde intermediate in the Wiesner synthesis of atisine^{2c} is illustrated in Scheme 4.



Scheme 4

In the case of the simplest 3-oxocyclohexaneacetaldehyde (Scheme 5), the C(3) two carbon side chain was introduced on 2-cyclohexen-1-one exploiting the classical diethylmalonate Michael addition,⁸ the same product was also obtained by the allylsilane Sakurai TiCl₄-mediated conjugate addition.⁹

Following the latter methodology, different monocyclic 3-oxo-cyclohexaneacetaldehydes were also synthesized.¹⁰

2. Cyclization of the 3-oxocyclohexaneacetaldehyde moiety

As pointed out in the Introduction, in this intramolecular aldol reaction the 3-oxo-cyclohexaneacetaldehyde nucleophilic C(4) adds to the electrophilic side chain formyl C-atom to give a C(6) epimeric mixture of 6-*endo*- and 6-*exo*-hydroxybicyclo[2.2.2]octan-2-ones which are in equilibrium through the parent ketoaldehyde (Scheme 1).¹¹

2.1 Reaction conditions

The cyclization can be carried out under acidic or basic catalysis. Being, in most cases, the last step of a cascade process, the first step of which constituted by the unmasking of a hidden hydroxyketone, acidic or basic reactions conditions were chosen upon necessity. Thus the cyclization has been performed in aqueous mineral acid,^{2a,2e} in aqueous mineral acids (HCl, H₂SO₄, H₃PO₄)/polar co-solvents (THF, acetone) mixtures,^{2b-d, 2f-h, 2l-m, 2o-p, 2r-s} in an organic acid (*p*-TsOH)/apolar solvent (CCl₄) mixture,¹² in methanolic NaOH^{2j} and in methanolic THF/NaOH solution.²ⁿ

2.2 *Endo/exo* products distribution under kinetic and thermodynamic conditions

The experimental reports related to above quoted cases do not disclose whether they were carried out under kinetic or thermodynamic conditions. Besides the analysis and separation of the epimeric product mixtures were not always performed. On these grounds a rigorous evaluation of the *endo/exo* epimers relative stability cannot be carried out.

Nevertheless obtaining the *endo* epimer as the major product after a long reflux in a THF/aqueous HCl mixture prompted Wiesner and coworkers to hypothesize that the *endo* epimer was the thermodynamic product.^{2f} This hypothesis was confirmed by the observation that when separately submitted to equilibration in THF/HCl both the *endo* and *exo* epimers give mixtures in which the former predominates.¹³

If the *endo* product could on these grounds reasonably be considered the thermodynamic product, it was not known which epimer was the kinetic product. Carrying out the reaction at various times, it was shown later that the *endo* epimer is both the kinetic and thermodynamic product.¹³

2.3 Factors controlling the equilibrium *endo/exo* product distribution

On Dreiding models inspection, H-bonding between the C(2)=O and HO-C(6) in the *endo* epimer appears unlikely. This assumption was confirmed by molecular mechanics (MM) calculations (Figure 1), X-ray (Figure 2) and NMR experiments (Figure 3).¹³

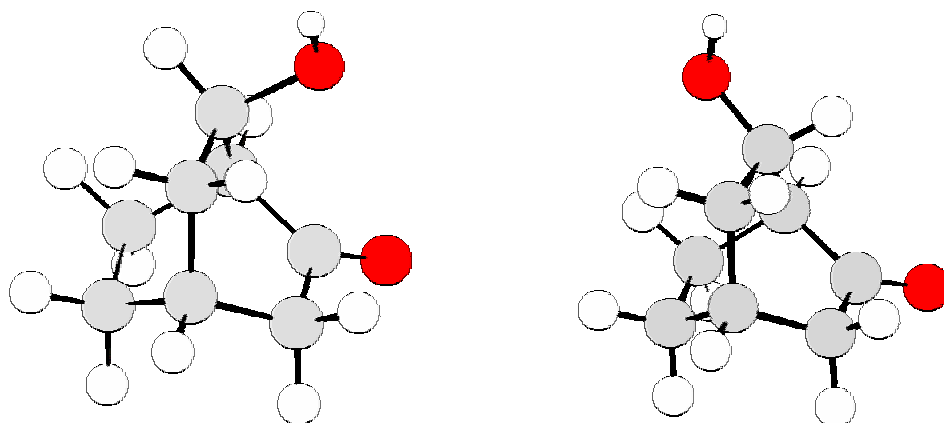


Figure 1. Optimized structures of 6-*endo* and 6-*exo*-hydroxybicyclo[2.2.2]octan-2-one.

X-ray experiments, carried out on the related methyl 13-*endo*-hydroxy-16-oxo-17-noratisan-18-oate (Figure 2), indicated the lack of the necessary spatial requirements for intramolecular H-bonding.¹⁴

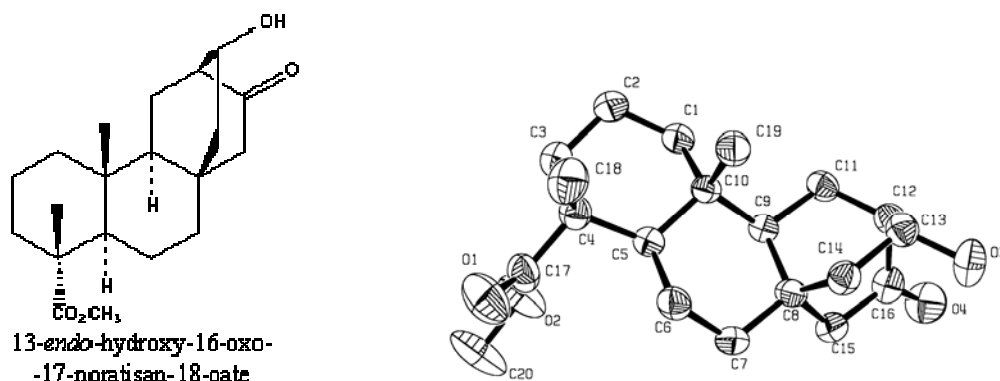


Figure 2. Structural formula and ORTEP-3 drawing of methyl 13-*endo*-hydroxy-16-oxo-17-noratisan-18-oate.

¹H-NMR experiments carried out on both epimers at different temperatures confirmed the lack of intramolecular H-bonding in 6-*endo*-hydroxybicyclo[2.2.2]octan-2-one, the chemical shift of the HO-C(6) of both epimers approaching similar high field values on temperature increase.

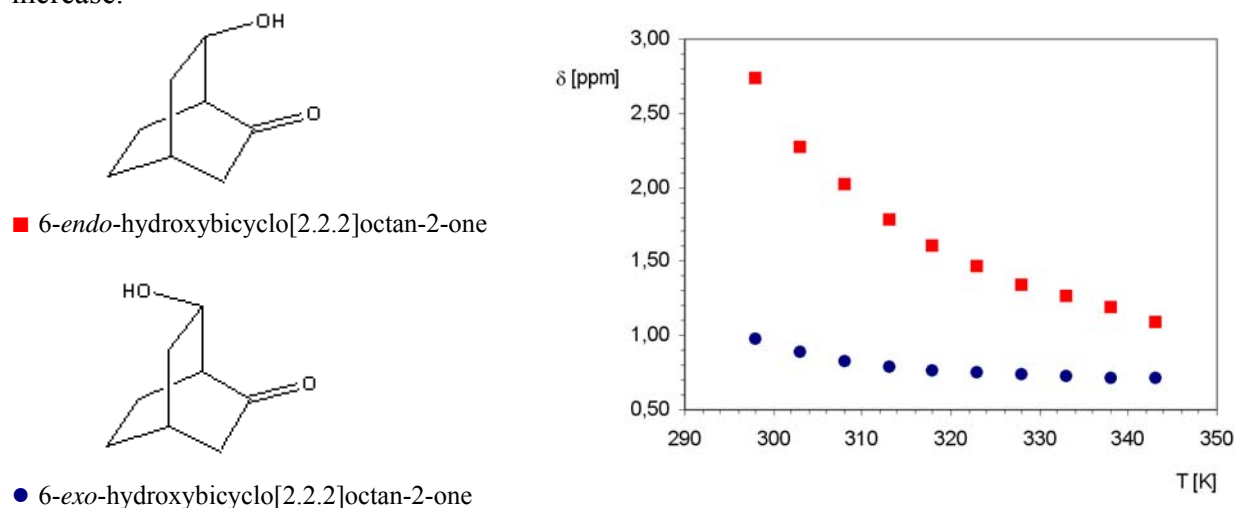


Figure 3. HO-C(6) chemical shifts (0.1 M in C₆D₆) for 6-*endo*-hydroxybicyclo[2.2.2]octan-2-one (■) and 6-*exo*-hydroxybicyclo[2.2.2]octan-2-one (●) at different temperatures.

Having ruled out an intramolecular H-bonding stabilization in the *endo* epimer, a geometric analysis to establish the destabilizing interactions in the *exo* epimer was carried out.

As could be inferred from molecular models, the C(1)-C(6)-C(5)-C(4)-C(8)-C(7) six membered ring in both epimers is fixed in a boat conformation. Thus, in accord with Ouellette and Booth,¹⁵ who compared the interactions between an *exo*-configured substituent at C(6) in

bicyclo[2.2.2]oct-2-ene and the $H_{\text{exo-C}(7)}$ to the 1,3 boat-axial interaction in cyclohexane, it was hypothesized that an interaction between the *pseudo*-axially oriented HO-C(6) and the $H_{\text{exo-C}(7)}$ might be present in the *exo* epimer. The interatomic distances values obtained by NOE difference spectra and MM calculations supported the hypothesis of a repulsive interaction between the two groups. From MM calculations resulted also that the *endo* epimer has a strain energy value 0.6 kcal/mol lower than the *exo* one.^{13,16}

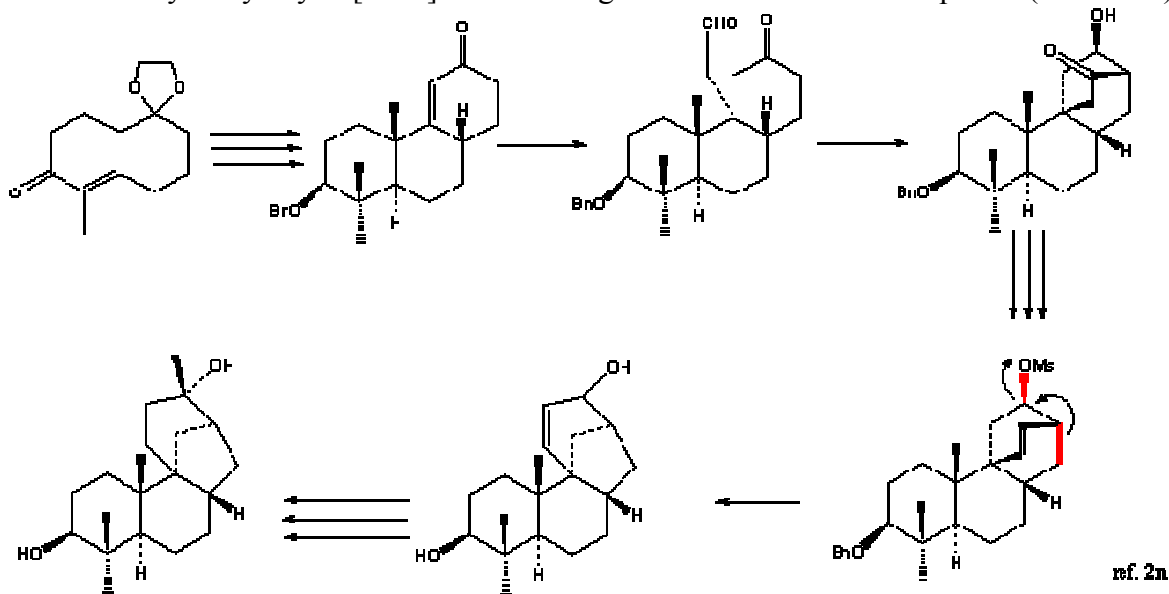
3. Applications to the synthesis of natural products

As pointed out above, the intramolecular aldol condensation of the 3-oxocyclohexanecetaldehydes was devised for the synthesis of natural products containing a bicyclo[2.2.2]octane moiety such as atisine,^{2a-c} atisirene,^{2d} trachylobane and related compounds.^{2g, 2s}

It has also been applied to the synthesis of natural products containing a bicyclo[3.2.1]octane moiety.^{2h-o, 2q} In fact the 6-hydroxybicyclo[2.2.2]octan-2-one emerging from the aldol condensation after being converted into a suitably substituted bicyclo[2.2.2]octan-2-ol might undergo to a [2.2.2]→[3.2.1] rearrangement. As known, the rearrangement proceeds with the migration of the C-C bond antiperiplanar to the leaving group. Thus a different leaving group location and stereochemistry produces a different skeleton. Clarifying in this respect are the syntheses of the tetracyclic diterpenes maritimidol,²ⁿ aphidicolin,^{2l, 2o} stemarin^{2k} and 13-stemarene.^{2q}

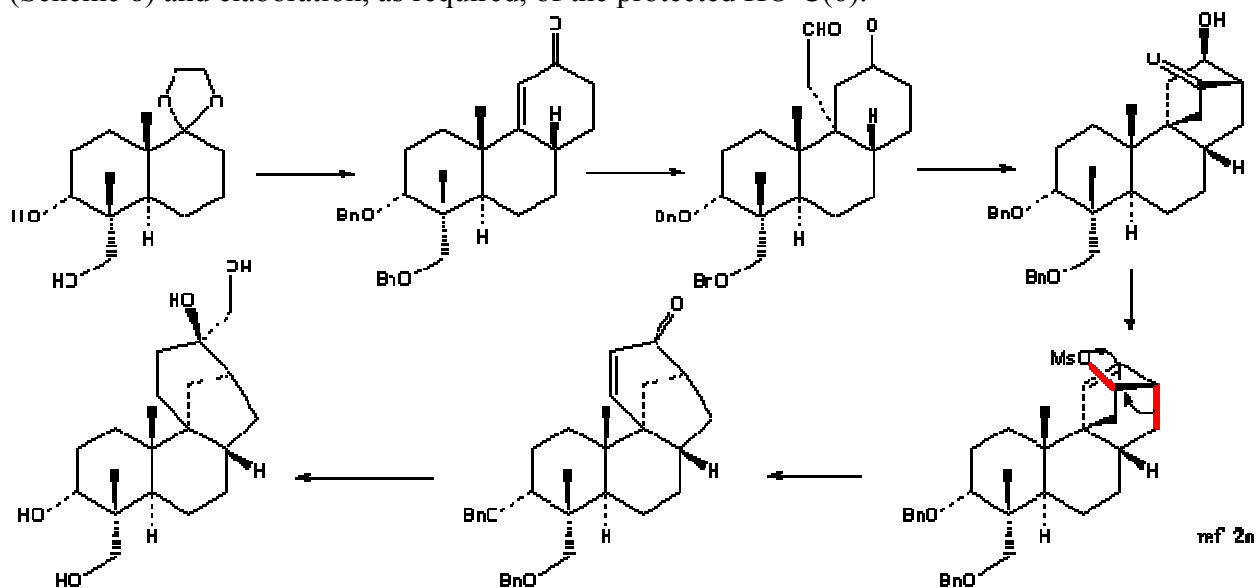
3.1 Preparation of the bicyclo[2.2.2]octanol moiety

3.1.1 Bicyclo[2.2.2]octanols in which the hydroxy group is *endo* to C(2).⁴ This is the simplest and easiest case, because the hydroxy group in the final product has the same stereochemistry of HO-C(6) of the major ketol (*endo* epimer) of the aldol condensation. Further elaboration of the parent 6-*endo*-hydroxybicyclo[2.2.2]octan-2-one gives then the desired compound (Scheme 5).



Scheme 5

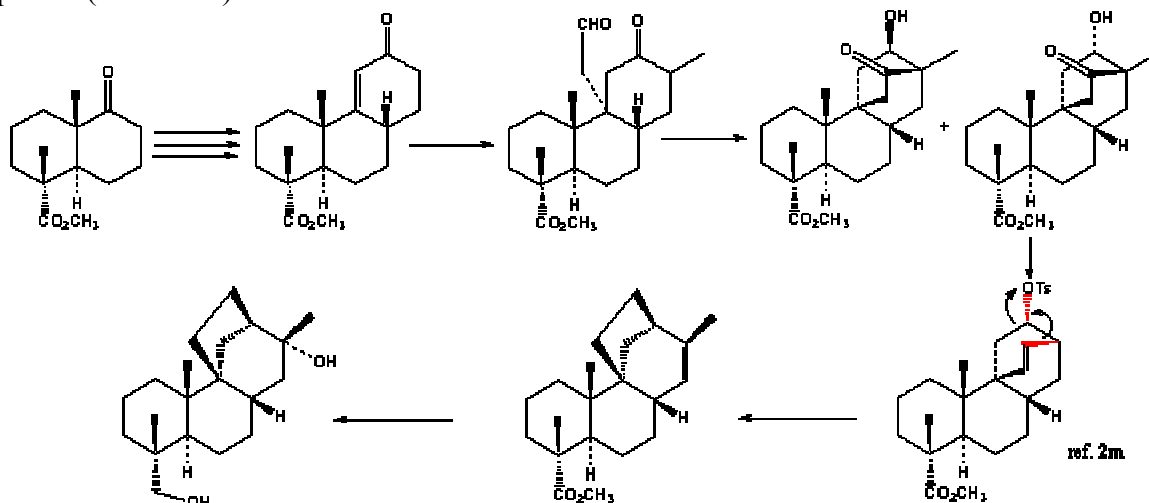
3.1.2 Bicyclo[2.2.2]octan-2-ols in which the hydroxy group is *endo* to C(6).⁴ The needed bicyclo[2.2.2]octan-2-ol might be obtained from the parent 6-*endo*-hydroxybicyclo[2.2.2]octan-2-one by protection of the *endo* HO-C(6) followed by diastereoselective reduction of the C(2)=O (Scheme 6) and elaboration, as required, of the protected HO-C(6).



Scheme 6

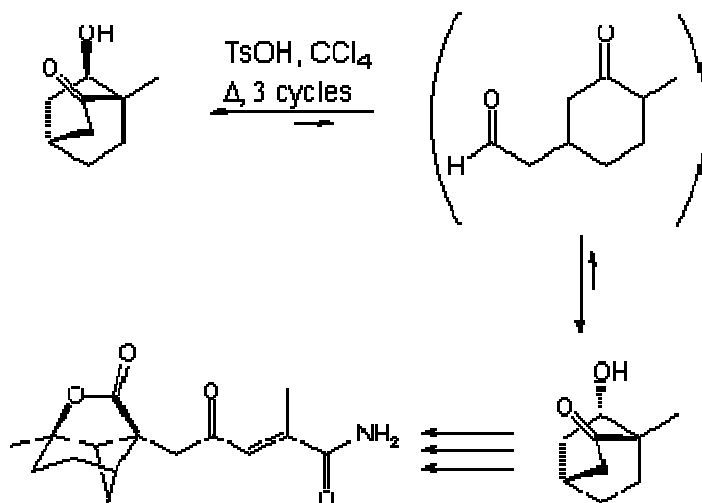
3.1.3 Bicyclo[2.2.2]octanols in which the hydroxy group is *exo* to C(2).⁴ In this case the hydroxy group in bicyclo[2.2.2]octanol has the same stereochemistry of the HO-C(6) of the minor epimer (*exo*) of the aldol condensation, that is opposite to that of the HO-C(6) of the major product (*endo* epimer) of the condensation. Three different tactics can be envisaged.

3.1.3.1 Deoxygenation (ethanedithiol, BF_3 , r.t.; Ni/Raney, EtOH, reflux) of the parent 6-*exo*-hydroxybicyclo[2.2.2]octan-2-one gives the desired compound.¹⁸ Of course the previous non-diastereoselective step (the intramolecular aldol condensation) is a flaw in the whole synthetic sequence (Scheme 7).



Scheme 7

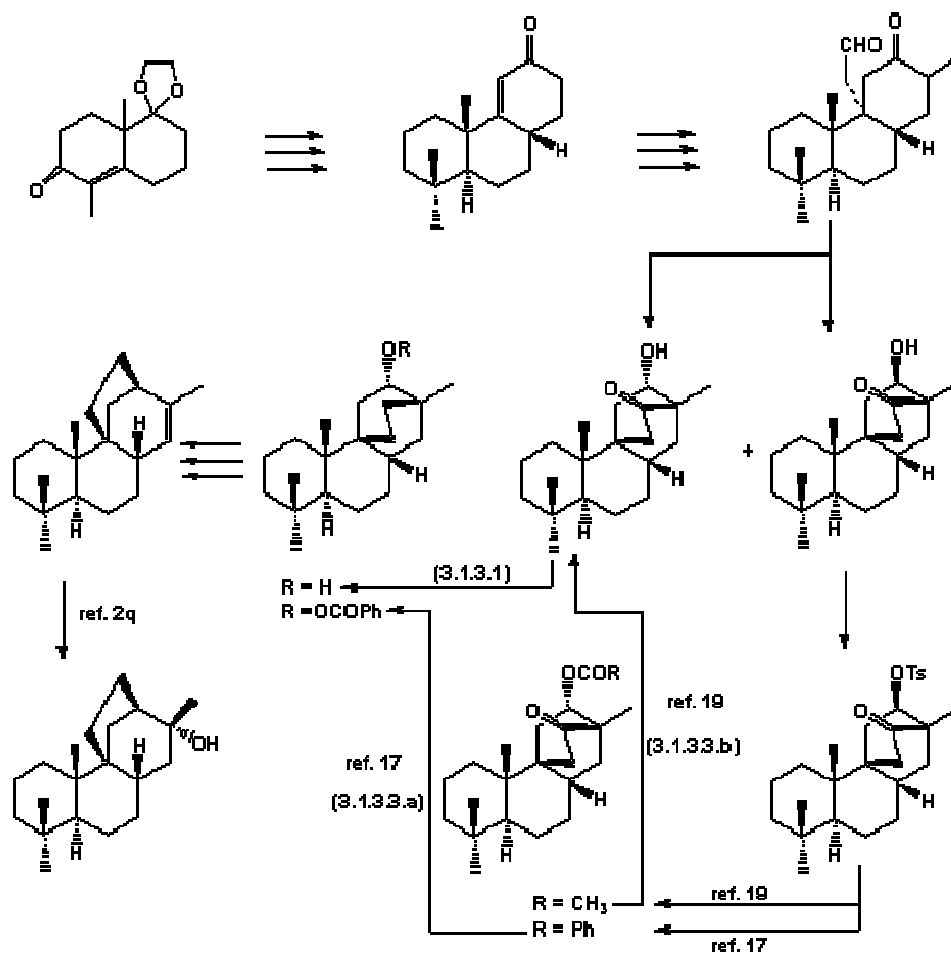
3.1.3.2 The 6-hydroxybicyclo[2.2.2]octan-2-ones mixture is separated, the minor 6-*exo*-hydroxybicyclo[2.2.2]octan-2-one collected and the major 6-*endo*-hydroxybicyclo[2.2.2]octan-2-one re-submitted to equilibration. The equilibrium mixture is then again separated and the minor epimer again collected. Some cycles are required, as in the Mori synthesis of (+)-pinthunamide¹² (Scheme 8).



Scheme 8

3.1.3.3 Conversion of the 6-*endo*-hydroxybicyclo[2.2.2]octan-2-one into the corresponding tosylate and treatment of the latter with a tetraalkylammonium carboxylate to give a 6-*exo*-carbalkoxybicyclo[2.2.2]octan-2-one¹⁹ in which the *exo* ketol system is locked and therefore unable to equilibrate back to the more stable *endo* epimer.

- Deoxygenation of the S_N2 reaction product, followed by basic hydrolysis gives then the desired bicyclo[2.2.2]octan-2-ol (Scheme 9).
- Recently, however, after R.S. Brown's disclosure that esters cleavage can be performed by methanolysis under non-basic conditions in the presence of La(OTf)₃,²⁰ an alternative sequence, implying deprotection of the 6-*exo*-acetoxybicyclo[2.2.2]octan-2-one by methanolysis in the presence of La(OTf)₃ to give a 6-*exo*-hydroxybicyclo[2.2.2]octan-2-one followed by deoxygenation, as described above, was put to work,²¹ thus allowing to improve the obtaining of a key intermediate in the syntheses of 13-stemarene and 18-deoxystemarin (Scheme 9).



Scheme 9

Conclusions

The intramolecular aldol condensation of 3-oxocyclohexaneacetaldehydes leading to C(6) epimeric mixtures of 6-hydroxybicyclo[2.2.2]octan-2-ones has been reviewed. Both steps, the preparation of the 3-oxocyclohexaneacetaldehyde moiety and its cyclization were examined as well as the *endo/exo* distribution under thermodynamic conditions and the factors responsible for it.

Applications of this reaction and further elaborations of the condensation products into a bicyclo[2.2.2]octan-2-ol in the frame of the synthesis of natural products were also considered. From this review it appears that a) an α,β -unsaturated cyclohexanone was always adopted as the starting material, b) only two methodologies (Claisen rearrangement and allene photoaddition) were chosen for the introduction of the formylmethyl side-chain in complex systems c) a way to obtain as a major product a 6-*exo*-hydroxybicyclo[2.2.2]octan-2-one by intramolecular aldol condensation of 3-oxocyclohexaneacetaldehyde has not been yet devised.

The field is therefore still open to further investigations. We hope the reader might agree and find this review useful.

Acknowledgements

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