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1,2,4-Trioxane in organic synthesis. Unusual entry to diverse carbocyclic frameworks derived from β-ionone

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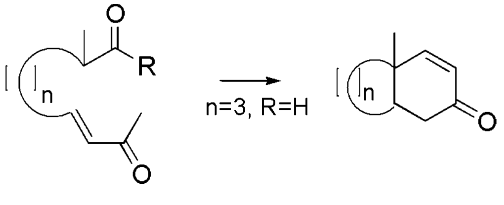
Abstract—Synthesis of [4.4.0]- or [5.3.0]-bicyclic frameworks was achieved via sequential intramolecular Michael/aldol and tandem intramolecular adol/aldol strategies, starting from acyclic precursors derived from β-ionone.

Carbocyclic ring construction is a fundamental process of organic synthesis. Particularly, structurally diverse bicyclic frameworks such as perhydroazulene and decalin systems are found in a large variety of natural products, many of which possess relevant biological activity.[1] Moreover, new rigid carbon framework densely functionalized can potentially be used as scaffolds for the synthesis of novel collections of compounds.[2] Many useful strategies based on the combination of classical and modified carbonyl reactions have been developed to access various carbocyclic frameworks. Several examples include Michael/aldol,[3] Michael/Claisen,[4] double/Michael,[5] and Michael/Dieckmann[6] annulations approach. In this context, there is a significant amount of precedence in the literature for the construction of bicyclo-[4.4.0] ring systems, by a sequential approach initiated by an intermolecular Michael addition followed by an intramolecular aldol reaction (Robinson annulation).[7] However, few reports dealt with the application of these sequential cyclization reactions, in an intramolecular version, starting from an acyclic precursor.[8]



Scheme 1.

Seminal studies by Stork's group have shown that when an intramolecular Michael addition is followed by an intramolecular aldol condensation, the sequence provides an excellent protocol for the preparation of *trans*-hydrindenone system, when an aldehyde-alkenone with three carbon tether is used as a substrate[9] (Scheme 1). The choice of the reaction conditions, mainly the nature of the base, exerts an important role in determining the reaction efficiency. The selectivity of the process was found to be highly dependent on the counterion of the base used.

Some problems associated to this process are the accessibility of suitable acyclic precursors that, due to its multifunctional nature, can potentially poses regio- and chemoselectivity problems.

Recently we have reported an easy access to triketones **1** derived from a rearrangement of trioxane 2.[10] This result strongly prompted as to investigate the intramolecular reactivity of **1** for the constructions of bicyclic systems, as an extension of our previous work aimed to explore and develop the synthetic potential of the 1,2,4-trioxane system (Scheme 2).

In this report, we would like to demonstrate the viability of the intramolecular Robinson annulation approach to bicyclo-[4.4.0] ring system, and also present some aspects of the reactivity of these acyclic precursors for the construction of highly functionalized carbocyclic frameworks.

Acyclic compounds **1** were obtained in good yield, by metal induced rearrangement of trioxane **2**, prepared from β-ionone (**3**).

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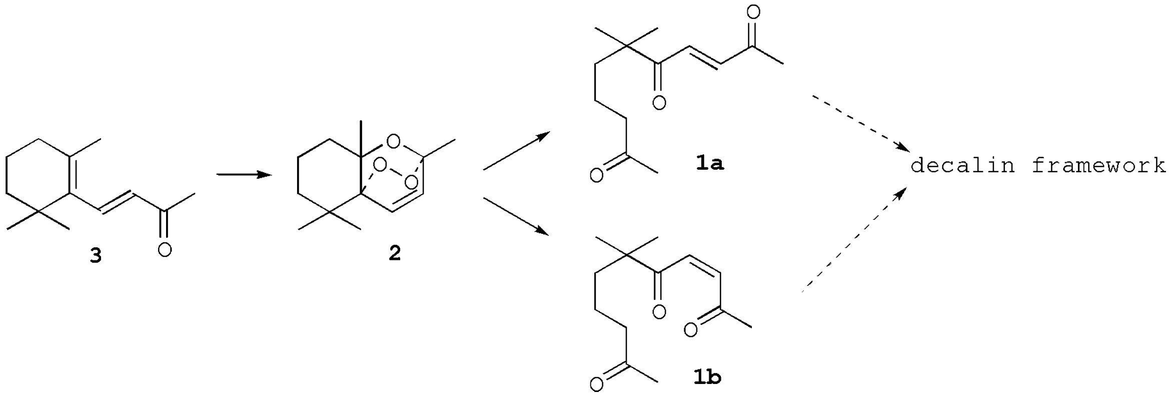
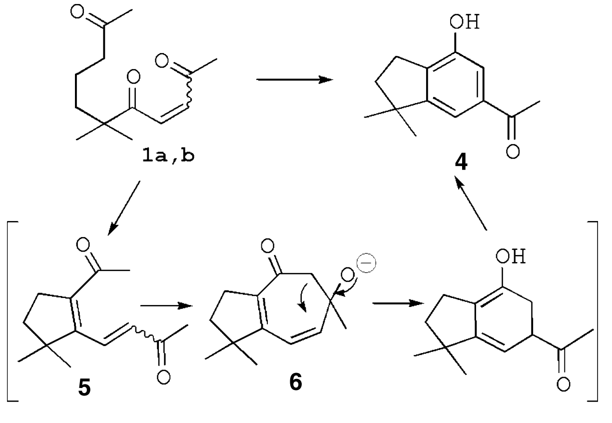


Scheme 2.

Preliminary experiments using common reaction conditions such as LiOH/acetone, MeONa/MeOH, failed to induce the desired tandem intramolecular Michael/aldol transformation. In the case of using LiOH/MeOH we were able to isolate an adduct with an structure that, based on its ^{1}H and ^{13}C NMR spectroscopic data correspond to compound **4**[11] (Scheme 3). Although the mechanism of formation of **4** is unclear a possible explanation is a chemoselective intramolecular aldol condensation of enedione-monoketone **1** that would give cyclopentendione **5** as reactive intermediate. Under the same conditions, **5** would undergo a second aldol condensation to generate the unsaturated keto-alkoxide **6**. The intermediate **6** could then afford **4**, via a vinylogous retro-aldol type cleavage and aromatization.[12] In view of these results, we assume that, under these conditions, the competitive intramolecular aldol condensation takes precedence over the desired intramolecular Michael addition.

In order to avoid the competitive aldol cyclization, attention was turned to explore the use of uncharged nitrogen bases. It was expected that the advantages of non-ionic bases such as milder reaction conditions and good solubility in organic solvent would lead to a site selective attack of initially formed carbanion to the Michael acceptor moiety.



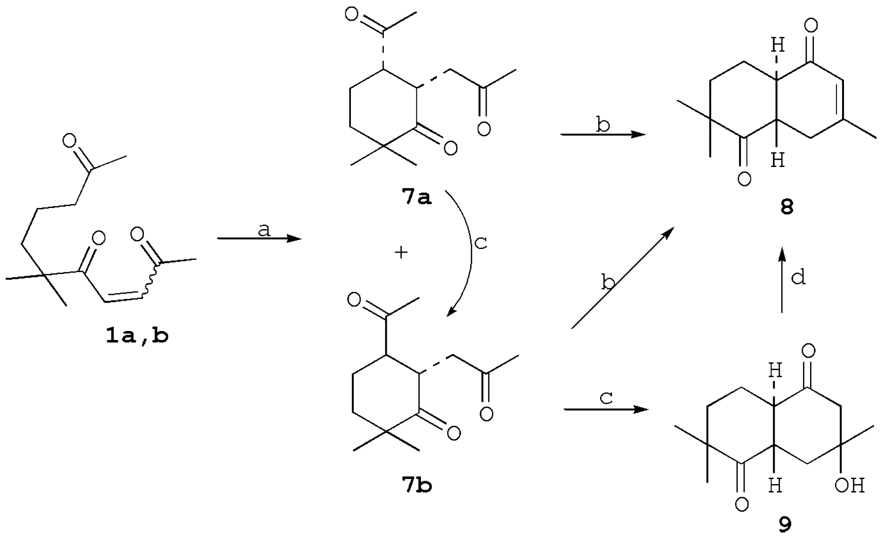
Scheme 3. *Reagents and conditions*: (a) Li(OH), MeOH, rt.

Accordingly, treatment of **1a** with DBU (1.2 equiv.) in 1,2-dichloroethane led to a smooth intramolecular Michael reaction affording the diastereomeric cyclohexanones **7a** and **7b** in 75% combined yield (Scheme 4). It must be noted that the sequence of addition—addition of DBU to a solution of **1** in 1,2-dichloroethane—significantly influenced the yield. Although the diastereoselectivity of this cyclization is poor, the two diastereomers could be easily separated by column chromatography (**7a** 40%, **7b** 35%).[11]

The structure of **7a** and **7b** were determined by analysis of their ^{1}H and ^{13}C NMR spectra and were confirmed by ^{1}H–^{1}H and ^{1}H–^{13}C COSY correlation experiments. Their stereochemical assigments were made on the basis of ^{1}H–^{1}H *J*-coupling values.[11]

With Michael adducts **7a**,**b** in hand we next investigated the intramolecular aldol reaction to the corresponding ring-closed products. After considerable experimentation, we found that the treatment of the diastereomers **7a** and **7b** separately under basic conditions (LiOH/MeOH), lead to the same product, the *trans*-enone **8**,[11] as a single stereoisomer (Scheme 4).

Several attempts to modify the outcome of the aldol condensation, in order to preserve the relative stereochemistry present in compounds **7a** and **7b** were unsuccessful. However, in the course of our studies on cyclizations procedures, we identified TBAF as an efficient reagent to promote the aldol condensation. The reaction of **7** proceed smoothly in the presence of stoichiometric amount of TBAF (1.0 equiv.), giving the cyclized β-hydroxyketone **9**[11] (Scheme 4). Further examination of the reaction conditions showed that the intramolecular aldol condensation takes place even in the presence of a catalytic amount of TBAF (0.1 equiv.). Under these conditions, compound **7b** gave a smooth reaction to **9**, in good yield. The other isomer **7a** gave, after much longer reaction time, the same cyclized reaction product **9**. We detected that, in this case, the reaction proceed through the initial transformation of **7a** into its *trans*-isomer **7b**, presumably via isomerization and/or retro Michael reaction and re-addition. We believe that unfavorable steric interactions prevents cyclization of **7a** to *cis*-bicyclic compound,



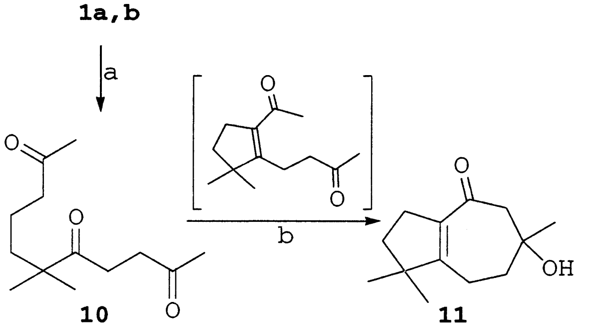
Scheme 4. *Reagents and conditions*: (a) DBU, $C_4H_2Cl_2$, 0°C–rt. (b) Li(OH), MeOH, rt. (c) TBAF, THF, rt. (d) $(Ac)_2O$, Et_3N, DMAP.

and only for compound **7b** the intramolecular aldol condensation can take place. Attempts of acetylation of **9** under standard conditions resulted in the formation of alkenone **8**, thus confirming the structure of **9**.

To our knowledge, the use of TBAF as a base in aldol condensation reactions has not been reported previously and may offer a route to improve efficiency in base catalyzed cyclizations.

In order to develop further the use of compound **1** for the synthesis of cyclic frameworks, the intramolecular cyclization of triketone **10**, obtained by selective reduction of **1**,[10] was investigated (Scheme 5).

We found that compound **10** cyclized by treatment with LiOH/MeOH to give the hydroazulenone **11**[11] in good yield (70%). The formation of **11** can be rationalized by a tandem process involving two sequential aldol condensations, taking place in one-pot reaction. The easy access to bicyclic compound **11** seems particularly attractive in the context of natural product as a valuable intermediate for synthetic applications.



Scheme 5. *Reagents and conditions*: (a) Zn/AcOH (b) Li(OH), MeOH, rt.

In summary, we showed that acyclic triketones **1** and **10**, can undergo intramolecular cyclizations allowing the access to functionalized monocyclic and bicyclic systems, with complete chemo- and regioselectivity, affording an interesting example of site-selective reactivity in a polyfunctional molecule. In this procedure, both of the two-fused rings of compounds **8**, **9** and **11** are newly constructed from the starting acyclic precursors employing sequential intramolecular Michael/aldol and tandem intramolecular aldol/aldol strategies, without the need of protecting groups neither the formation of enol-derivatives. These sequential cyclocondensations procedures represent an alternative synthetic strategy for building up carbocyclic frameworks, that can be extended to other conveniently substituted acyclic precursors. Overall, this process can be regarded as a way of restructure[13] monocyclic β-ionone skeleton into fused [4.4.0]- or [5.3.0]-bicyclic systems, via the intermediacy of the easily obtained trioxane **2**.

Acknowledgements

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11. *Selected spectral data*. **4**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.46 (brs, 1H), 6.81 (brs, 1H), 2.84 (t, $J=6$ Hz, 2H), 2.30 (s, 3H), 1.97 (t, $J=6$ Hz, 2H), 1.20 (s, 6H). ^{13}C NMR: 18.94 (t), 20.87 (q), 24.08 (2q), 35.69 (t), 41.21 (s), 120.11 (d), 120.20 (d), 127.14 (s), 132.06 (s), 136.75 (s), 153.08 (s), 204.05 (s). **7a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.44 (ddd, $J=3.2$, 8.26, 12.12 Hz, 1H), 2.78 (m, 1H), 2.59 (dd, $J=8.19$, 17.03 Hz, 1H), 2.25 (dd, $J=3.37$, 17.03 Hz, 1H), 2.19 (s, 3H), 2.18 (3H s), 1.87–1.62 (m, 4H), 1.21 (s, 3H), 1.03 (s, 3H). ^{13}C NMR: 24.53 (q), 24.81 (t), 24.98 (q), 28.79 (q), 30.12 (q), 39.42 (t), 40.62 (t), 42.99 (d), 44.23 (s), 56.0 (d), 206.77 (s), 208.43 (s), 214.17 (s). HRMS: *m*/*z* calcd for $C_{13}H_{20}O_3$ (M^+): 224.1412. Found: 224.1406. **7b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.34 (brs, 1H), 3.21 (brs, 1H), 3.17 (dd, $J=7.0$, 14.0 Hz, 1H), 2.34 ($m_{centered}$, 1H), 2.21 (s, 3H), 2.13 (s, 3H), 2.01–1.87 (m, 2H), 1.60–1.42 (m, 2H), 1.18 (s, 3H), 1.06 (s 3H). ^{13}C NMR: 23.79 (t), 25.24 (q), 26.62 (q), 28.95 (q), 30.31 (q), 35.65 (t), 41.0 (t), 42.62 (d), 44.06 (s), 54.63 (d), 207.41 (s), 209.50 (s), 212.41 (s). Anal. Calcd. For: $C_{13}H_{20}O_3$: C, 69.91; H, 8.99. Found: C, 69.63; H, 9.17%. **8**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.89 (brs, 1H), 2.95 (ddd, $J=14.5$, 10.0, 5.3, Hz, 1H), 2.62–2.44 (m, 2H), 2.37–2.17 (m, 2H), 1.99 (s, 3H), 1.90–1.58 (m, 3H), 1.18 (s, 3H), 1.08 (s, 3H). ^{13}C NMR: 20.34 (t), 24.17 (q), 24.82 (q), 25.02 (q), 31.0 (t), 38.85 (t), 44.22 (s), 46.53 (d), 50.86 (d), 125.38 (d), 160.53 (s), 198.50 (s), 213.84 (s). Anal. calcd for: $C_{13}H_{18}O_2$: C, 75.68; H, 8.8. Found: C, 75.47; H, 9.00%. **9**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.13 (ddd, $J=13.1$, 11.8, 3.5 Hz, 1H), 2.41 (brs, 2H), 2.24 ($m_{centered}$, 1H), 2.10 ($m_{centered}$, 1H), 1.97–1.70 (m, 4H), 1.54 ($m_{centered}$, 2H), 1.41 (s, 3H), 1.18 (3H, s), 1.07 (3H, s). ^{13}C NMR: 20.30 (t), 25.09 (q), 25.20 (q), 30.96 (q), 37.52 (t), 38.88 (t), 44.69 (s), 45.80 (d), 53.69 (t), 54.66 (d), 73.07 (s), 208.32 (s), 214.37 (s). **11**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.83 (ABquartet, $\Delta\delta_{AB}$: 0.13, $J=13$ Hz, 2H), 2.60–2.10 (m, 4H), 2.05–1.60 (m, 4H), 1.34 (s, 3H), 1.08 (s, 3H), 1.05 (s, 3H). ^{13}C NMR: 22.65 (t), 25.32 (q), 25.66 (q), 28.79 (t), 30.16 (q), 37.55 (t), 42.29 (t), 49.36 (s), 57.23 (t), 70.93 (s), 137.80 (s), 168.38 (s), 196.46 (s). HRMS: *m*/*z* calcd for $C_{13}H_{20}O_2$ (M^+): 208.14633. Found: 208.14561.
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