A concise organocatalytic and enantioselective synthesis of isotetronic acids†

Jean-Marc Vincent,* Chrystèle Margottin, Muriel Berlande, Dominique Cavagnat, Thierry Buffeteau and Yannick Landais*

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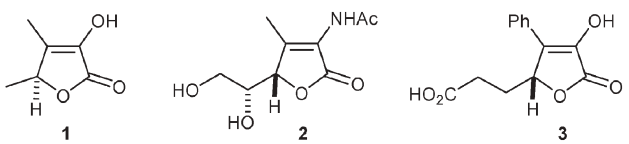
A concise enantioselective route to isotetronic acids using an organocatalyzed aldol reaction between α-oxocarboxylic acids and aldehydes has been developed, leading to the titled compounds in reasonable yields and good enantioselectivities.

Isotetronic acids are ubiquitous in Nature and exhibit a wide range of biological activities. Their simple butenolide structural motif has also attracted a lot of interest as a building block in syntheses of complex natural products, such as erythronolide A and tetrotoxin.[1] Sotolon **1**,[2] found in both racemic and enantioenriched form in raw sugarcane, fenugreek seeds or botrytized wine, (+)-leptosphaerin **2**,[3] a metabolite isolated from marine fungi *leptosphaeria oraemaris*, or WF-3681[4] **3** isolated from *chaetomella raphigera* and exhibiting aldose reductase inhibitory activity constitutes some representative members of this family (Scheme 1). Other natural and more complex butyrolactones have recently been described that possess promising antiproliferative activity against various carcinoma thus justifying the interest for this class of targets.[5]

Numerous strategies have been devised to access these butenolides.[6] Enantioselective approaches based on chiral pool synthesis using carbohydrates, amino-acids and ascorbic acid were shown to afford the titled compounds in an enantiomerically pure form, but these approaches generally suffer from long synthetic sequences.[7] Diastereoselective and catalytic enantioselective strategies have also been described. Copper-bisoxazoline and proline have been used as chiral inducers in aldol reactions involving pyruvates both as carbonyl donors and acceptors.[8] While high level of enantioselectivities were generally attained, the scope of these reactions were limited to pyruvate acceptors. Based on these premises, it was anticipated that the key furanone skeleton **I** in butenolides **1–3** could be assembled in a one-pot operation through an organocatalyzed aldol type reaction between a reactive



Scheme 1 Naturally occurring isotetronic acids.

University Bordeaux-1, CNRS-UMR 5255, Institut des Sciences Moléculaires, 351, cours de la libération, 33405, Talence, France. E-mail: jm.vincent@ism.u-bordeaux1.fr; y.landais@ism.u-bordeaux1.fr; Fax: (+33) 540006286; Tel: (+33) 540002289

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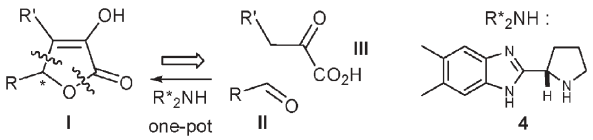
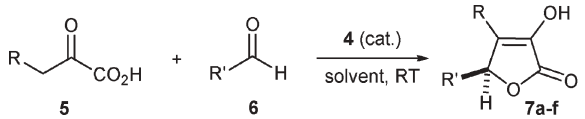


Scheme 2 Isotetronic acids through BIP (**4**)-catalyzed aldol reaction.

α-ketoacid **III** and an aldehyde **II** acting respectively as carbonyl donor and acceptor (Scheme 2). Organocatalyzed aldol reactions have been the subject of a tremendous development in the last few years and a wealth of data is now available.[9] In this context, we disclose here our preliminary results on aldol reactions between α-ketoacids **5** and a series of aldehydes **6** using the benzoimidazole-pyrrolidine **4**, a proline surrogate that was recently designed in our laboratory as an efficient organocatalyst for a number of amino-catalyzed processes.[10]

Oxo-butyric acid ethyl ester was used in preliminary studies but soon appeared as a poor substrate. Much better yields were obtained using directly α-ketoacids **5** which were finally used throughout the investigation (Table 1). 10 mol% catalyst was used during this work, except with poorly reactive aromatic aldehydes which required the use of 30 mol%. Oxo-butyric acid **5** (R′ = Me) was used as the model carbonyl donor. Several aldehydes were tested and showed that both aromatic and aliphatic aldehydes led to promising results. Better yields and enantioselectivities were observed with aromatic substrates, particularly those having electron-withdrawing groups (C_6F_5 or *p*-NO_2Ar) (entries 9, 11, 12).[11] It should to be noted that proline proved to be a poor catalyst for this transformation. In a reaction run in DMSO using L-proline (10 mol%), the reactive *p*-nitrobenzaldehyde and oxobutyric acid afforded **7e** in only 26% yield and 36% ee. Electron-rich aromatic aldehydes provided both lower yields and ee (entries 13–15). Isobutyraldehyde led to **7a** in moderate yields but excellent enantioselectivity in good agreement with pioneering studies which showed that branched aliphatic aldehydes are good substrates for amino-catalyzed aldol reactions (entries 1–4).[12] In line with this result, acetaldehyde led only to a trace amount of sotolon **1**. Increasing the reactivity of the aldehyde using ethyl glyoxylate (entry 5) led to **7b** in good yield but surprisingly to no enantioselectivity. Substitution of the ethyl group for a *t*-Bu led to a similar result. Steric hindrance however plays an important role in this aldol reaction when the bulky group is close to the reactive carbonyl function as shown with pivalaldehyde which gave no reaction even after 5 days at rt (entry 6). The nature of the solvent was also varied and we observed that the reaction was equally efficient in water when liquid or viscous aldehydes were employed

Table 1 Isotetronic acids synthesis through an aldol process mediated by organocatalyst **4**



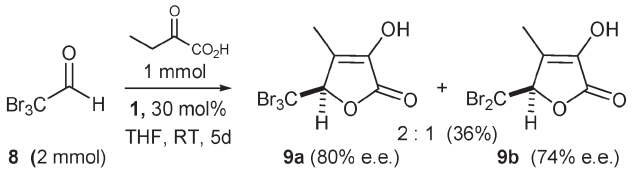
Entry	R	R′	Mol% **4**	Product	Solvent	*t*/d	Yield[a] (%)	ee[b] (%)
1	Me	^{i}Pr	10	**7a**	THF[c]	4	44	76
2	Me	^{i}Pr	10	**7a**	DMF	4	30	80
3	Me	^{i}Pr	10	**7a**	H_2O	4	26	87
4	Me	^{i}Pr	10	**7a**	DCM	4	<5	90
5	Me	CO_2Et	10	**7b**	THF	4	63	0
6	Me	tBu	10	**7c**	THF	5	—	—
7	Me	Ph	10	**7d**	THF	4	90	70
8	Me	Ph	10	**7d**	H_2O	4	65	68
9	Me	*p*-$NO_2C_6H_4$	10	**7e**	THF	4	77	83
10	Me	*p*-$NO_2C_6H_4$	10	**7e**	H_2O	6	—	—
11	Me	C_6F_5	10	**7f**	THF	5	77	84
12	Me	C_6F_5	30	**7f**	H_2O–THF[d]	5	69	90
13	Me	*p*-BrC_6H_4	30	**7g**	THF	5	60	67
14	Me	*p*-$MeOC_6H_4$	30	**7h**	THF	7	10	36
15	Me	*p*-$MeOC_6H_4$	10	**7h**	H_2O	7	20	63
16	H	*p*-$NO_2C_6H_4$	10	**7i**	THF	10	<5	—
17	Ph	C_6F_5	30	**7j**	THF	5	45	87
18	Et	C_6F_5	10	**7k**	THF	5	71	90

[a] Isolated yields. [b] ee estimated from chiral HPLC. [c] Anhydrous THF. [d] THF (100 μL) was added to the reaction mixture to facilitate the stirring.

(entries 3, 8, 12, 15). This is worthy of note as enantioselectivity in most cases is also significantly improved in such media (entries 3, 12, 15). This may be indicative of a hydrophobic effect amplifying the chiral organocatalysis.[13] Better stabilization of the polar transition state (*vide infra*) by water may also be invoked. Recently, a few examples of enamine-based organocatalyzed aldol processes were reported for which good enantioselectivities were effectively observed when the reactions were run in water[13,14] or in the presence of water.[15,16] This seems to be the case in this study where the aldehydes do not dissolve homogeneously in water.

The aldol process was successfully extended to other α-ketoacids such as phenylpyruvic and 2-oxovaleric acids (entries 17, 18). Starting from pentafluorobenzaldehyde the corresponding butenolides **7j** and **k** were obtained in moderate to good yields and good enantioselectivities. Surprisingly, under the same conditions, pyruvic acid provided the expected isotetronic acid **7i** but only in trace amount (entry 16). Interestingly, efficient enantioenrichment can be achieved by simple recrystallization. For instance, enantiomerically pure **7f** (entries 11 and 12) was obtained after a recrystallization by slow diffusion of hexane vapours into a toluene solution of **7f** (initial ee 84%). Similarly, **7k** (entry 18) can be isolated almost enantiomerically pure (ee 98%) by crystallization from the crude reaction mixture.

The aldol process was also extended to more reactive α,α,α-tribromoaldehyde **8** which led to the desired butenolide **9a** in modest yield but good enantioselectivity, along with the debrominated butenolide **9b** (Scheme 3). Similar enantioselectivity of both products suggest that debromination occurred only after the aldol reaction. This result is noteworthy as **9a** and **b** are separable and may be functionalized further to provide enantioenriched aliphatic isotetronic acids that are difficult to obtain



Scheme 3 Aldol reaction with tribromoacetaldehyde **8**.

using a direct aldol reaction between **5** and the corresponding linear aldehydes.

Absolute configuration of isotetronic acids was obtained through vibrational circular dichroism (VCD) associated with *ab initio* calculations (*vide infra*). VCD is a well-established method for determination of absolute configuration and solution conformation of chiral molecules.[17] The method entails comparison of the observed VCD spectrum with spectra calculated at the density functional theory (DFT) level for conformers of a specified absolute configuration.[18] Because enantiomers have VCD intensities of opposite sign for each vibrational mode, the VCD spectrum provides a unique and rich signature of the absolute configuration.

VCD spectrum of isotetronic acid **7f** (R′ = C_6F_5), was recorded in $CDCl_3$ as solvent. Calculations of optimized geometry, vibrational frequencies, absorption, and VCD intensities were calculated by Gaussian 03 program at the DFT level with the B3PW91 functional and cc-pVTZ basis set for two conformations of the (*R*)-**7f** (R′ = C_6F_5) isomer. Indeed, the monomer of **7f** can assume two conformations that differ by a 180° rotation of the COH group, labeled $\mathbf{7f_a}$ (the hydroxyl group points toward the methyl group) and $\mathbf{7f_b}$ (the hydroxyl group points toward the ketone group) (Fig. 1). On the other hand, B3PW91/cc-pVTZ calculations predict that the fluoro phenyl group is locked nearly perpendicular to the furanone ring, due to the steric repulsion between the fluorine atom and both the oxygen atom and the methyl substituent of the five-membered ring. The optimized structures and relative Gibbs energies calculated for the two conformers are shown in Fig. 1. $\mathbf{7f_b}$ is the most stable conformer and its relative population is almost 100% at room temperature. The calculated VCD spectrum for the $\mathbf{7f_b}$ conformer is compared to experiment in Fig. 2, where the experimental intensities have been adjusted to 100% ee. The computed VCD spectrum reproduces fairly well the intensity and the sign of the bands observed in the experimental spectrum, allowing the definitive determination of the (*R*) configuration and the conformation ($\mathbf{7f_b}$) for **7f** and by analogy to other isotetronic acids **7a–k**.

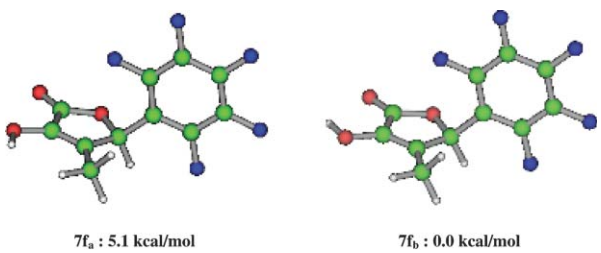


Fig. 1 Optimized structures and relative Gibbs energies of (*R*)-**7f** (R′ = C_6F_5) conformations.

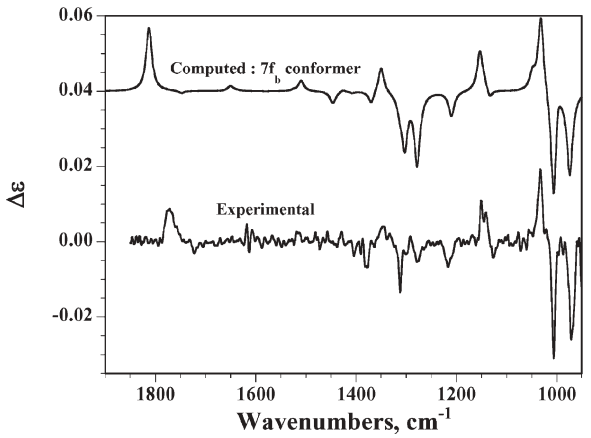
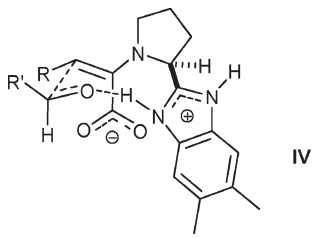


Fig. 2 Comparison of the experimental VCD spectrum of **7f** (ee 90%, R′ = C_6F_5) in $CDCl_3$ solution with the computed VCD spectrum of the **7f$_b$** conformer.



IV

Fig. 3 Transition state model for catalyst **4**-mediated aldol reaction.

This configuration may be rationalized invoking a chair-like transition state as illustrated in Fig. 3. Protonation of the benzoimidazole ring by acid **5** likely provides a zwitterionic species **IV** which carboxylate moiety participates to the stabilization of the assembly, explaining the high level of enantioselectivity.

In summary we have described along these lines a new access to isotetronic acids, a class of butenolides with relevant biological activities. The method is straightforward and may be applied to a wide range of aldehydes, leading to moderate to good yields of the desired compounds with good level of enantioselectivity. Interestingly, the reaction may also be performed in water affording the butenolides in some cases with improved enantioselectivities.

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