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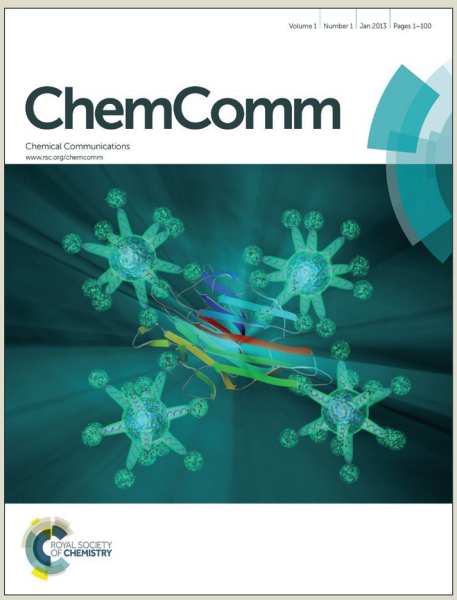

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The Evans Aldol–Prins cyclization: a general and stereoselective method for the synthesis of 2,3,4,5,6-pentasubstituted tetrahydropyrans

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A general and stereoselective method to synthesize 2,3,4,5,6-pentasubstituted tetrahydropyrans in three steps starting from three different aldehydes is described. Key substrates β,γ-unsaturated *N*-acyloxazolidin-2-ones were submitted to an "Evans Aldol–Prins" protocol to generate five σ-bonds and five stereocenters in an only one-pot process with yields up to 60% and excellent stereoselectivities.

The tetrahydropyran (THP) ring is a structural motif widely present in natural products (NPs) from marine and terrestrial sources, which exhibit varied bioactivity such as antibiotic, insecticidal, antiparasitic, vasoconstrictor, antitumor and so on.[1] Fused THPs constitute the skeleton of neurotoxic ladder toxins,[2] and non-fused THPs are also found in the core of NPs such as those shown in Fig. 1. For example, clavosolide A was isolated from the cytotoxic extract of the marine sponge *Myriastra clavosa*.[3] On its behalf, kendomycin, which was isolated from several *Streptomyces* strains, exhibits antiosteoporotic and antibiotic activity; its challenging structure has inspired several synthetic works.[4] Besides being part of bioactive NPs, it has been probed that the THP ring can also show bioactivity itself.[5] The plenty of NPs containing a THP ring has motivated the development and application of many synthetic strategies to achieve its synthesis, and among them, the Prins cyclization[6] has emerged for the last years as a powerful and versatile tool to access to valuable THPs.[7] For the last years, our research group has employed the Prins reaction to synthesize differently substituted six- and seven-membered oxa- and aza-heterocycles.[8] Highly substituted THPs such as those contained in the NPs of the Fig. 1 are the most challenging since a synthetic point of view.

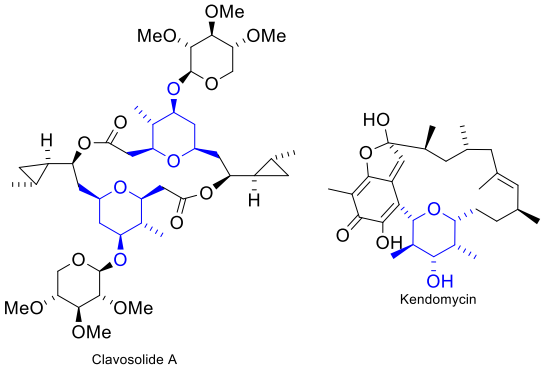

Fig. 1 Densely substituted tetrahydropyrans in natural products.

However, the application of the Prins cyclization to access 2,3,4,5,6-pentasubstituted THPs has been barely studied.[9] To the best of our knowledge, no systematic and profound studies directed towards the synthesis of 2,3,4,5,6-pentasubstituted THPs have been developed to date. This absence of a general method encouraged us to perform a complete study to yield these treasured structures, covering both the nature and the stereochemistry of the substituents owned by the THP ring. As shown in the retrosynthetic analysis of Scheme 1, we envisioned a novel Evans Aldol–Prins (EAP) strategy[10] which should enable the access to all-*trans* 2,3,4,5,6-pentasubstituted THPs like **1** in a stereoselective fashion, starting from β,γ-unsaturated alcohols bearing a *N*-acyloxazolidin-2-one in α position (**2**). Prins cyclization of alcohol **2** would allow to install a heteroatom in the position 4 of the THP ring, as well as different substituents R^3 in the position 6. In addition, highly enantiopure *syn*-alcohol **2**[11] could be obtained through the Evans protocol.[12] Moreover, this aldol addition permits the introduction of a wide variety of substituents R^2 in alcohol **2**, and therefore in the position 2 of the THP **1**. Both enantiomers of alcohol **2**, and consequently both enantiomers of THP **1**, could be synthesized adjusting the stereochemistry of the precursor *N*-acyloxazolidin-2-one **3**.

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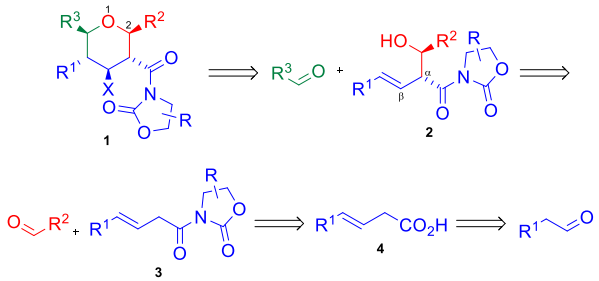
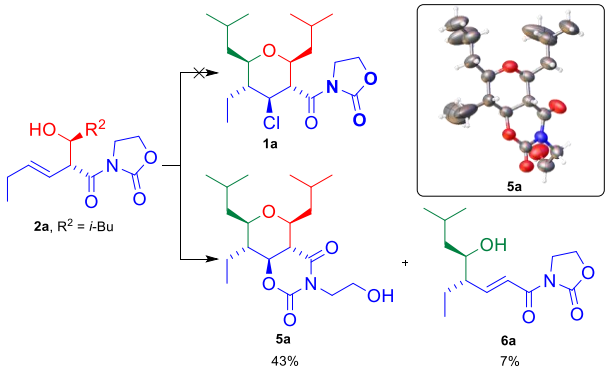
† Electronic Supplementary Information (ESI) available: general experimental methods, experimental procedures, compound characterization, NMR spectroscopic data and crystallographic data for compound **5a** (CCDC 1442874). See DOI: 10.1039/x0xx00000x



Scheme 1 Retrosynthetic analysis to access to 2,3,4,5,6-pentasubstituted THPs

Substrates like **3** are easily obtainable from commercial oxazolidin-2-ones and the corresponding β,γ-unsaturated carboxylic acid (**4**).[13] Readily available acids **4**[14] bear the carbonyl moiety and the substituent R^1 that will exhibit the THP **1** in the position 3 and 5, respectively. Before testing the chiral version of the proposed strategy, we decided to evaluate its efficacy, and the tolerance to different substituents, employing the less expensive non-chiral oxazolidin-2-one as Evans auxiliary. Thus, herein we report our advances in the general and diastereoselective synthesis of 2,3,4,5,6-pentasubstituted THPs via this innovative EAP protocol.

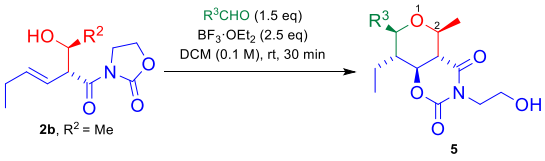
Heartened by previous results obtained in our research group, and with the structure of the 4-chloro-THP **1a** in mind, we decided to start our study with the racemic homoallylic *syn*-alcohol **2a** (Scheme 2). It was submitted to a Prins cyclization catalyzed by the well-known system $Fe(acac)_3$/TMSCl.[8] Surprisingly, instead of the expected product **1a**, we isolated the unprecedented bicyclic product **5a**, along with a small amount of the by-product **6a**, obtained as a result of the competitive 2-oxonia-Cope rearrangement.[15] This Prins cyclization was very diastereoselective since **5a** shows all the substituents of the THP ring in equatorial positions (an all-*trans* disposition), as it is illustrated by the values of the *J*-coupling over 9 Hz,[16] GOESY experiments and X-ray crystallography. Compound **5a** exhibits an unique tetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione core as result of an endocyclic ring cleavage of the *N*-acyloxazolidin-2-one.[17] These fragmentations to yield 1,3-oxazinane-2,4-diones appears in the literature,[18] although, to the best of our knowledge, this is the first example of this



Scheme 2 Unexpected synthesis of a bicyclic structure through the Prins cyclization

moiety attached to a THP ring. Moreover, 1,3-oxazinane-2,4-diones are associated with some promising bioactivities such as anti-epileptic and analgesic.[19] Encouraged by the novel and biologically relevant core of compounds **5**, and as they are 2,3,4,5,6-pentasubstituted THPs themselves, which therefore satisfy our original goal, we decided to direct our efforts to their synthesis. After an extensive search, we discover that an excess of $BF_3{\cdot}OEt_2$ was the best promotor to perform the Prins cyclization, obtaining bicycles **5** with no traces of the undesired rearranged by-product **6**. With optimized conditions in hand, we decided to check the robustness of the Prins cyclization introducing different groups R^3 in the C_6 of the THP ring, and *syn*-alcohol **2b** was selected as starting material to test several aldehydes (Table 1). In entry 1 it is shown that **2b** was transformed into the corresponding bicycle **5b** with a pleasing 78% yield, a really exceptional result considering that four new σ-bonds (three C-O bonds and one C-C bond) are created in just one step. In addition to the excellent yield, it should be highlighted that three new contiguous stereocenters were generated in only one step, yielding **5b** as an only product between eight possible diastereoisomers. However, it is well-known that when secondary homoallylic alcohols like **2** bearing a R^2 group and aldehydes such as R^3CHO with $R^3 \neq R^2$ are submitted to a Prins cyclization, several THPs might be obtained as result of the chain exchange associated to the competitive 2-oxonia-Cope rearrangement.[15b] Gratifying, the expected bicycles were obtained, with no traces of other undesired THPs, from alcohol **2b** and a wide and heterogeneous range of aldehydes (Table 1, entries 2-12). Thus, this "two-steps EAP" tactic yields THPs bearing linear and bulky aliphatic chains, triple bonds, α,β-unsaturations, an acid-sensitive cyclopropane, electron-poor aromatic groups carrying F, Cl and Br (in *meta*-, *orto*- and *para*- positions respectively) and an electron-rich aromatic moiety.

Table 1 Scope of aldehydes



2b, R^2 = Me — **5**

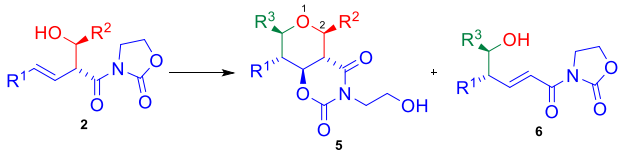
Entry	R^3	Product	Yield[a] (%)
1	Me	**5b**	78
2	Bu	**5c**	69
3	*i*-Bu	**5d**	70
4	$HC{\equiv}C(CH_2)_3$	**5e**	65
5	$HC{\equiv}C(CH_2)_2$	**5f**	60
6	n-$C_5H_{11}C{\equiv}C$	**5g**	46[b]
7	*c*-Pr	**5h**	63
8	Ph	**5i**	72
9	3-F-Ph	**5j**	64
10	2-Cl-Ph	**5k**	60
11	4-Br-Ph	**5l**	68
12	4-(MeO)-Ph	**5m**	63

[a] Isolated yield; >95:5 dr determined by ^{1}H NMR spectroscopy, unless noted otherwise. [b] 90:10 dr.

Afterwards, we decided to broaden the scope of the protocol by modifying the substituents R^1, R^2 and R^3 (Table 2). At first, we decided to run the original reaction shown in Scheme 2 (R^2 = R^3 = *i*-Bu) with the optimized conditions, obtaining **5a** with a noticeable improvement of the yield from 43 to 78% (entry 1). Bicycles with different aliphatic chains were also successfully obtained (entries 2 and 3). When we started from alcohol **2d** (R^2 = Ph), the desired THP **5p** was obtained in low yield, and it was accompanied by bicycle **5b** as the mayor product, due to the stabilization of the intermediate obtained after the 2-oxonia-Cope rearrangement (entry 4).[15] By contrast, when the aromatic group was separated from the aldehyde by a two-units methylene bridge, the yield of **5q** improved to the usual values (entry 5). Aldol **2f** (R^1 = H) led to the bicycle **5r** with a yield of 38%, a significant drop compared with the yield of 78% achieved when there was an ethyl group in that position (R^1 = Et, see entry 1 in Table 1). Additionally, it was also isolated the 2-oxonia-Cope by-product **6b** (R^1 = H, R^3 = Me) with a 40% of yield. When we explored the reactivity of the challenging starting alcohol **2f** facing aromatic aldehydes, we obtained bicycles **5s** and **5t** with similar yields (entries 7 and 8).

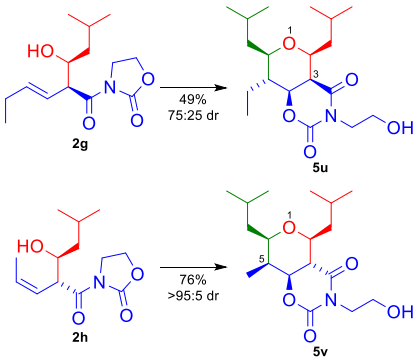
Compounds **5r**-**5t** are 2,3,4,6-tetrasubstituted THPs, and all their functional groups adopt an equatorial position in the ring, hence they share the same substitution patron that is shown by the core of clavosolide A (Fig. 1). At this point, we wondered if our methodology could also allow the access to the challenging core of kendomycin, in which all substituents are installed in equatorial positions except the *meta*-substituent in relation to the oxygen embedded in the THP ring (Fig. 1). Thus, we decided to study the effect of the isomerism of the starting alcohol in the Prins cyclization to get the desired axial *meta*-substituent related to the oxygen (Scheme 3).

Table 2 Synthesis of differently substituted bicycles[a]



Entry	Aldol	R^1	R^2	R^3	Product	Yield[b] (%)
1	**2a**	Et	*i*-Bu	*i*-Bu	**5a**	78
2	**2c**	Et	Bu	Bu	**5n**	66
3	**2c**	Et	Bu	*i*-Bu	**5o**	50
4	**2d**	Et	Ph	Me	**5p**	35[c,d]
5	**2e**	Et	CH_2CH_2Ph	Me	**5q**	54[c]
6	**2f**	H	Me	Me	**5r**	38[e]
7	**2f**	H	Me	Ph	**5s**	39[c,f]
8	**2f**	H	Me	Ar[g]	**5t**	41[f]

[a] Reaction conditions: R^3CHO (1.5 eq), $BF_3{\cdot}OEt_2$ (2.5 eq), DCM (0.1 M), rt, 30 min. [b] Isolated yield; >95:5 dr determined by ^1H NMR spectroscopy, unless noted otherwise. [c] 90:10 dr. [d] It was also obtained a 55% of **5b** with >95:5 dr. [e] 40% of **6b** (R^1 = H, R^3 = Me) was also isolated. [f] 14% of **5r** was also detected, as result of the releasing of ethanal to the medium after 2-oxonia-Cope rearrangement; rearranged by-product **6** was also detected by ^1H NMR spectroscopy. [g] Ar = 3,4-$(MeO)_2Ph$.

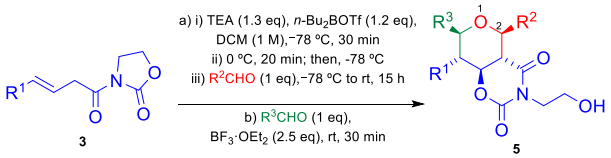


Scheme 3 Effect of the isomerism of the starting alcohol in the Prins cyclization. Reaction conditions: *i*-BuCHO (1.5 eq), $BF_3{\cdot}OEt_2$ (2.5 eq), DCM (0.1 M), rt, 30 min.

To this effect, we firstly performed the Prins cyclization employing the *anti*-aldol **2g**,[20] and bicycle **5u**, in which C_3 bears the substituent in an axial orientation, was obtained. Secondly, we modulated the geometry of the olefin in the starting material. As expected,[21] the *Z*-homoallylic alcohol **2h** yielded the bicycle **5v**, bearing an axial methyl group at C_5. Therefore, our methodology also provides properly the access to the THP core of kendomycin.

The above described "two-steps EAP" strategy allows the rapid access to 2,3,4,5,6-pentasubstituted THPs (**5**) in just two steps starting from *N*-acyl oxazolidin-2-ones (**3**). However, we conceived an even simpler strategy to achieve the target THPs: the "one-pot EAP" protocol, in which *N*-acyl oxazolidin-2-ones (**3**) were consecutively subjected to the Evans aldol addition and to the Prins cyclization, without isolating the aldol products (Table 3). This one-pot variation allowed us to synthesize bicycle **5b** starting from the *N*-acyl oxazolidin-2-one **3a** (R^1 = Et, entry 1), with a comparable yield to that obtained through the "two-steps EAP".[22] Driven by the motivation, we straightaway tested the access to THPs owning different aliphatic and aromatic substituents attached to the 2, 5 and 6 positions (entries 2-8).

Table 3 One-pot conversion of β,γ-unsaturated *N*-acyl oxazolidin-2-ones into bicycles



Entry	R^1	R^2	R^3	Product	Yield[a] (%)
1	Et	Me	Me	**5b**	54
2	Et	n-$C_{13}H_{27}$	Me	**5w**	41
3	Et	*i*-Bu	Me	**5x**	42
4	Et	Bu	Ph	**5y**	31[b]
5	$PhCH_2$	Bu	Bu	**5z**	32
6	*n*-pentyl	Me	Bu	**5aa**	31
7	*n*-pentyl	Bu	Me	**5ab**	30
8	$BnOCH_2CH_2$	Me	Me	**5ac**	54[c]
9	Et	*i*-Bu	*i*-Bu	**5a**	60[d]

[a] Isolated yield; >95:5 dr determined by ^1H NMR spectroscopy, unless noted otherwise. [b] 90:10 dr. [c] Obtained as a 1.3/1 mixture of the benzylated/debenzylated THPs. [d] 5.3 grams were obtained with 85:15 dr.

Eventually, to evaluate the potential utility of this "one-pot EAP" methodology for a synthetic purpose, we decided to carry out a model reaction on a 4.5 gram scale (entry 9). To our pleasure, 5.3 grams (60%) of bicycle **5a** were obtained, a comparable yield as that previously achieved in the two-steps approach.[23] Although all yields ranged from 30 to 60%, it should be emphasized that this "one-pot EAP" methodology permits the straightforward synthesis of 2,3,4,5,6-pentasubstituted THPs (**5**) from *N*-acyl oxazolidin-2-ones (**3**) through a process in which five new σ-bonds are generated (three C-O bonds and two C-C bond). And last, but no least, five contiguous stereocenters are built in a very stereoselective way starting from a molecule with no chiral centers, and only one racemic pair was mainly obtained between sixteen possible racemic diastereoisomers.

In summary, this novel Evans Aldol–Prins methodology constitute the first general method to synthesize valuable 2,3,4,5,6-pentasubstituted THPs from β,γ-unsaturated *N*-acyl oxazolidin-2-ones. A panoply of substituents can be introduced in the THP ring, and the fine tuning of the stereochemistry of the starting aldol permits the synthesis of THPs with different spatial disposition. We expect that this methodology becomes a useful tool in the synthesis of complex natural products. Further investigation, such as the enantioselective version, mechanistic studies, derivatization and biological evaluation of the bicycles, are currently under development in our laboratory, and will be reported in due course.

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22 Prins cyclization of the alcohol **2b** (R^1 = Et, R^2 = Me) yielded **5b** with a 78% yield (table 1, entry 1); as described in ESI, starting alcohol **2b** was synthesized from **3a** (R^1 = Et) with a 75% yield. Thus, the global yield of this process after two steps was 59%.
23 Prins cyclization of the alcohol **2a** (R^1 = Et, R^2 = *i*-Bu) yielded **5a** with a 78% yield (table 2, entry 1); as detailed in ESI, starting alcohol **2a** was synthesized from **3a** (R^1 = Et) with a 81% yield. Thus, the global yield of this process after two steps was 63%.

