Synthesis of Bicyclic Hemiacetals Catalyzed by Unnatural Densely Substituted γ-Dipeptides

Maddalen Agirre,[∇] Tamara Bello,[∇] Jinxiu Zhou, María de Gracia Retamosa,* and Fernando P. Cossío*

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The asymmetric synthesis of bicyclic highly substituted tetrahydropyrans is described. The reaction is catalyzed by unnatural γ-dipeptides based on densely substituted L- and D-proline derivatives. This organocatalytic one-pot reaction takes place among a ketone, a nitroalkene, and an aldehyde to yield an octahydro-2H-chromene scaffold. Monomeric species, from which the corresponding γ-dipeptides are synthesized, cannot catalyze the reaction, thus confirming the emergent nature of the catalytic behavior of these dimeric species.
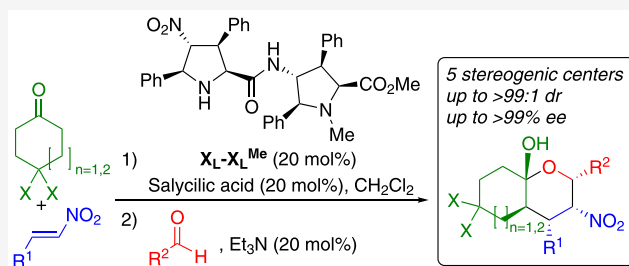
Tetrahydropyrans (THPs) are important structural six-membered oxygenated heterocycles that incorporate up to five stereogenic centers. In particular, fused THPs, including one or two octahydro-8aH-chromen-8a-ol units, are found in natural products. For instance, Figure 1 includes compounds
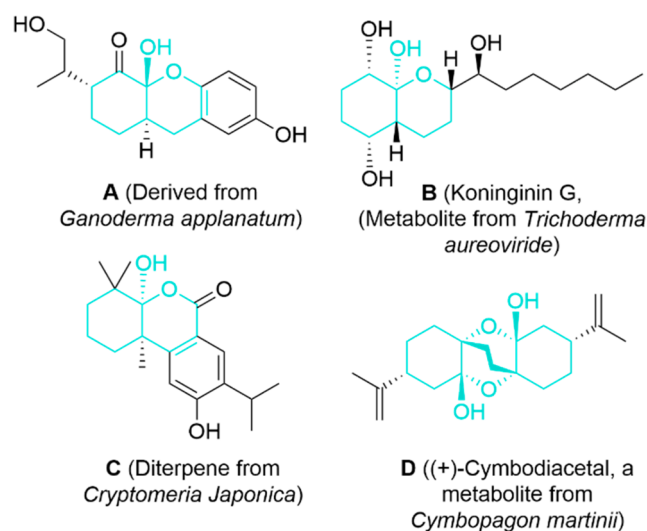

Figure 1. Several examples of natural products containing one or two octahydro-8aH-chromen-8a-ol units (colored cyan).

A (Derived from *Ganoderma applanatum*)

B (Koninginin G, (Metabolite from *Trichoderma aureoviride*)

C (Diterpene from *Cryptomeria Japonica*)

D ((+)-Cymbodiacetal, a metabolite from *Cymbopagon martinii*)

A,[1] **B**,[2] **C**, and **D**.[3,4] In addition, some of them are biologically active, such as diterpene **C**, which inhibits androgen receptor transcriptional activity in prostate cancer cells.[5]

Several methods have been developed for the construction of chiral THP structures,[6,7] among which asymmetric organocatalysis deserves special attention.[8] Cordova's group reported in 2005 the first organocatalytic synthesis of THPs employing iterative aldol reactions.[9] Enders et al. also published an interesting work on the organocatalytic synthesis of mono-cyclic 3-acetyl-2-hydroxy-5-nitro-THPs.[10] It is noteworthy that there is only one example of the synthesis of cyclohexane-fused 2-unsubstituted THPs by using cyclohexanone and 2-nitro-prop-2-en-1-ols in a two-component hemiketalization reaction.[11] In addition, the Michael–Henry–hemiketalization reaction has scarcely been investigated. It was not until 2011 that Hayashi and co-workers described a one-pot Michael–Henry–acetalization starting from nitroalkenes and two different aldehydes to yield mixtures of α- and β-anomeric monocyclic THPs.[12] In 2015, an organocatalytic kinetic resolution of racemic secondary nitroallylic alcohols via a Michael–hemiketalization sequence was reported to give densely substituted monocyclic tetrahydropyran-6-ols.[13] However, to the best of our knowledge, no Michael–Henry–hemiketalization reaction for the synthesis of fused THPs has been described in the literature.[14]

We have previously described the synthesis via (3+2) cycloadditions of densely substituted proline esters and their abilities as organocatalysts.[15] We found that unnatural L-*exo*-4-amino 2-carboxy O$_2$N-X$_L$ species [**1** (Figure 2)] are efficient catalysts for aldol reactions[16] and for a particular three-component cyclization.[17] In contrast, compounds of type **1** were unable to catalyze conjugate additions between ketones and nitroalkenes. However, amino derivatives H$_2$N-X$_L$ **2** (Figure 2) proved to be suitable organocatalysts for both
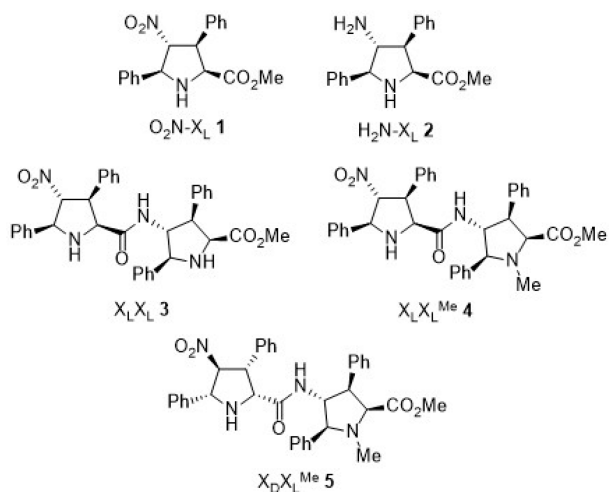
Figure 2. Monomeric (**1** and **2**) and dimeric (**3**−**5**) unnatural proline organocatalysts used in this work.

aldol and Michael reactions.[18] More recently, we have found that γ-dipeptides **3**−**5** possessing 4-nitro terminal groups exhibit catalytic properties, which can promote the three previously commented reactions with excellent yields and stereoselectivities.[19] On the basis of DFT calculations, we interpreted these results in terms of a favorable combination between the enamine catalytic site of one unit of the dipeptide

(HOMO-enhancing effect on the ketone) and the protonated pyrrolidine unit of the other component (LUMO-lowering effect on the Michael acceptor).

In view of these precedents, we envisioned the possible chemical synthesis of fused THP octahydro-2H-chromene scaffolds by the Michael−Henry−hemiketalization one-pot reaction starting from ketones, nitroalkenes, and aldehydes, as shown in Table 1. Initially, the three starting reagents were mixed together to yield traces of the aldol product corresponding to the competitive aldol reaction between cyclohexanone **6a** and ethyl glyoxylate **8a**. Monomeric pyrrolidines **1** (O$_2$N-X$_L$) and **2** (H$_2$N-X$_L$) were inactive for this reaction (Table 1, entries 1 and 2, respectively). In contrast, the reaction promoted by dipeptide **3** (X$_L$X$_L$) showed reasonable reaction times for the conjugate addition. In addition, the Henry−hemiketalization step was completed within 6 h, and the final product was obtained in good yield, good diastereomeric ratio, and excellent enantiomeric excess (entry 3). Increasing the catalytic load and using 4-nitro-benzoic acid accelerated the conjugate addition step, but a loss of diastereoselectivity was observed (entry 4). It is interesting to note that partial loss of selectivity after completion of the reaction in the presence of acetic acid has been reported.[20] These results were improved in terms of ee when dimeric catalyst **4** (X$_L$-X$_L$^{Me}), with only one active enamine precursor catalytic site, was employed (entry 5). Inversion of configuration in the pyrrolidine ring that possesses the NH

Table 1. Screening of Various Densely Substituted Prolines and Bases for the Optimization of the Michael−Henry−Hemiketalization Reaction[a,b]

entry	catalyst	base	t$_1$ (h)	t$_2$ (h)	dr[c]	yield[d] (%)	ee[e] (%)
1	**1** (O$_2$N-X$_L$)	Et$_3$N	48	240	nd	<5	nd
2[f]	**2** (H$_2$N-X$_L$)	Et$_3$N	48	216	nd	<5	nd
3	**3** (X$_L$X$_L$)	Et$_3$N	48	6	85:15	73	93
4[g]	**3** (X$_L$X$_L$)	Et$_3$N	16	6	75:25	70	91
5	**4** (X$_L$X$_L$^{Me})	Et$_3$N	24	6	80:20	47	99
6	**5** (X$_D$X$_L$^{Me})	Et$_3$N	144	6	84:16	69	−63
7[g]	**4** (X$_L$X$_L$^{Me})	Et$_3$N	24	6	>99:1	72	99
8[g]	**4** (X$_L$X$_L$^{Me})	DIPEA	24	168	nd	<5	nd
9[g]	**4** (X$_L$X$_L$^{Me})	DBU	24	48	50:50	53[h]	96
10[g]	**4** (X$_L$X$_L$^{Me})	DBU[i]	24	48	<1:99	65	98
11[g]	**4** (X$_L$X$_L$^{Me})	DABCO	24	48	nd	30	65

[a]The first step was conducted using ketone **6a** (1.0 mmol) and trans-β-nitrostyrene **7a** (1.1 mmol) in the presence of 10 mol % catalyst and 20 mol % salicylic acid (SA). The second step was conducted using aldehyde **8a** (2.0 mmol) and 20 mol % Et$_3$N. nd denotes not determined. [b]Reactions were monitored by ^{1}H NMR, and mixtures were stirred at room temperature until the starting materials were totally consumed (>99% conversion). [c]dr refers to (2S,3R,4S,4aR,8aS)-**10aaa**:(2S,3S,4S,4aR,8aS)-**10aaa'** ratios (different configurations of the chiral centers in the α-position with respect to the nitro group) and determined by ^{1}H NMR analysis of the crude mixture. [d]Isolated yield, after purification by column chromatography of **10aaa**. [e]Determined by HPLC with a chiral stationary phase. [f]With 30 mol % catalyst and 30 mol % p-nitrobenzoic acid. [g]With 20 mol % catalyst. [h]Yields refer to the sum of both diastereomers. [i]With 1 equiv of DBU.
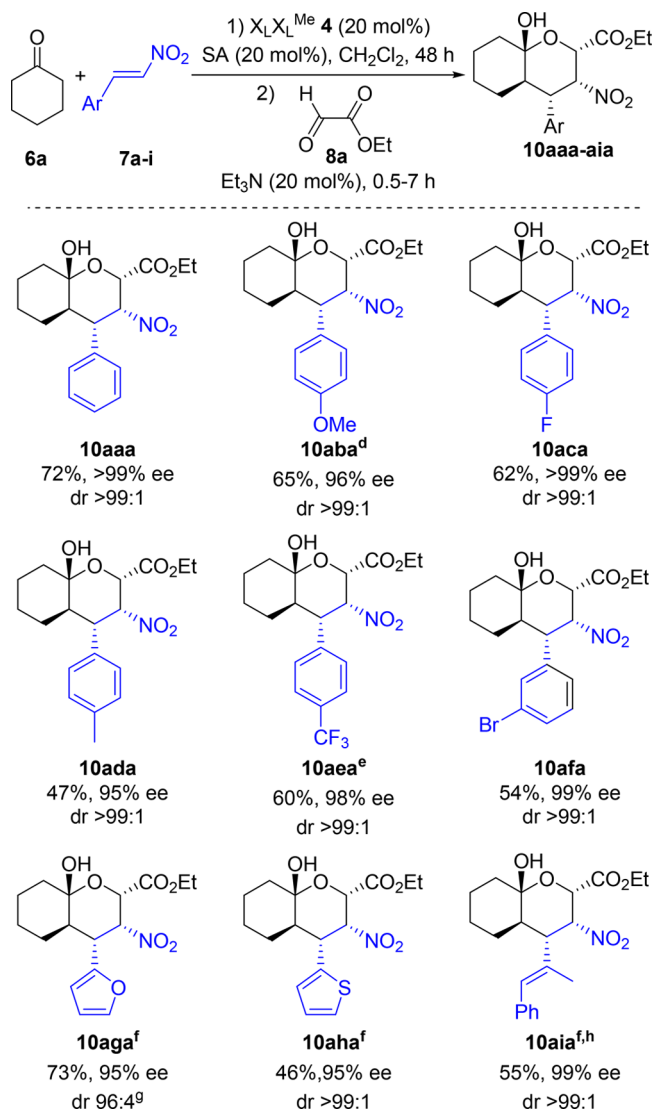
group required for the formation of the enamine nucleophile (catalyst **5**, X_D-X_L^{Me}) resulted in longer reaction times, and despite the good diastereomeric ratio, the yield and ee values decreased significantly, with inversion of configuration in final product **10aaa**. This latter result is compatible with a Michael step that determines the final stereochemical outcome and a partial mismatching between both D- and L-pyrrolidine units, thus resulting in a lower ee. Increasing the catalytic load to 20 mol % allowed us to obtain THP adduct **10aaa** as the sole product in good yield and excellent enantiomeric excess (entry 7). Final experiments comprised the study of the effect of the base in the reaction. None of the tested basic additives could improve the results obtained with Et₃N (entry 7). Treatment with DIPEA and DABCO entailed long cyclization times (entries 8 and 11, respectively), and the use of DBU resulted in two diastereomeric species (entry 9, vide infra for further details). When 1 equiv of DBU was used, the other diastereomeric species was isolated with 65% yield and 98% ee (entry 10). The structure and stereochemistry of both kinetically and thermodynamically favored products (**10aaa** and **10aaa′**, vide infra) were confirmed by X-ray diffraction analysis (see the Supporting Information). Interestingly, neither proline and several derivatives nor diamine organocatalysts could sufficiently promote this reaction efficiently (see the Supporting Information for further details).

Having determined the best reaction conditions, we investigated the scope of this process by evaluating several nitroalkenes while keeping the other two components **6a** and **8a** constant. The reaction proceeded smoothly in the presence of dimeric catalyst **4** with aromatic and heteroaromatic nitroalkenes **7a–h** (Scheme 1). While aliphatic conjugated nitroalkene **7i** was also convenient for this transformation yielding adduct **10aia** in moderate yield and excellent ee, aliphatic nitroalkene (*E*)-(2-nitrovinyl)cyclohexane **7j** provided only the intermediate Michael adduct in low conversion (<20%) after reaction for 7 days.

DFT calculations on the **6a** + **7a** + **8a** → **10aaa** reaction in the presence of NMe₃ and SA (see the Supporting Information) provided a suitable model of the sequence of events that leads to the final product from the nitronate derived from intermediate Michael adduct **9aa**. The stereochemistry of this intermediate is determined by the chiral organocatalyst. In turn, the facial discrimination of aldehyde **8a** stems from this intermediate. From these calculations (see Figure S1), we concluded that the role of the base and the acidic additive is essential for determining the viability of the reaction and its stereochemistry.

The reaction also worked with other cyclic ketones such as cycloheptanone **6b** and 1,4-cyclohexanedione monoethylene acetal **6c**. However, small changes were necessary to obtain the corresponding cycloadducts (Scheme 2). Derivative **10baa** demanded equimolar amounts of Et₃N for the total consumption of the γ-nitroketone intermediate. The corresponding adduct **10baa** was obtained in moderate yield and high enantioselectivity, but in a 92:8 mixture of inseparable diastereomers. The synthesis of **10caa** required 7 days for the Michael step to reach full conversion. Attempts to shorten the reaction time by increasing the temperature to 45 °C resulted in the formation of sluggish mixtures. The following Henry–hemiketalization step, on the contrary, was completed in 1 h. The desired THP derivative **10caa** was obtained as a single diastereomer in 62% yield and 87% ee. Unfortunately, when tetrahydro-4*H*-pyran-4-one **6d** and cyclohexane-1,3-dione **6e**

Scheme 1. Enantioselective Michael−Henry−Hemiketalization Reaction with Cyclohexanone, Ethyl Glyoxylate, and Various Nitroalkenes, Catalyzed by Dimeric Pyrrolidine $X_L X_L^{Me a-c}$

10aaa
72%, >99% ee
dr >99:1

10aba[d]
65%, 96% ee
dr >99:1

10aca
62%, >99% ee
dr >99:1

10ada
47%, 95% ee
dr >99:1

10aea[e]
60%, 98% ee
dr >99:1

10afa
54%, 99% ee
dr >99:1

10aga[f]
73%, 95% ee
dr 96:4[g]

10aha[f]
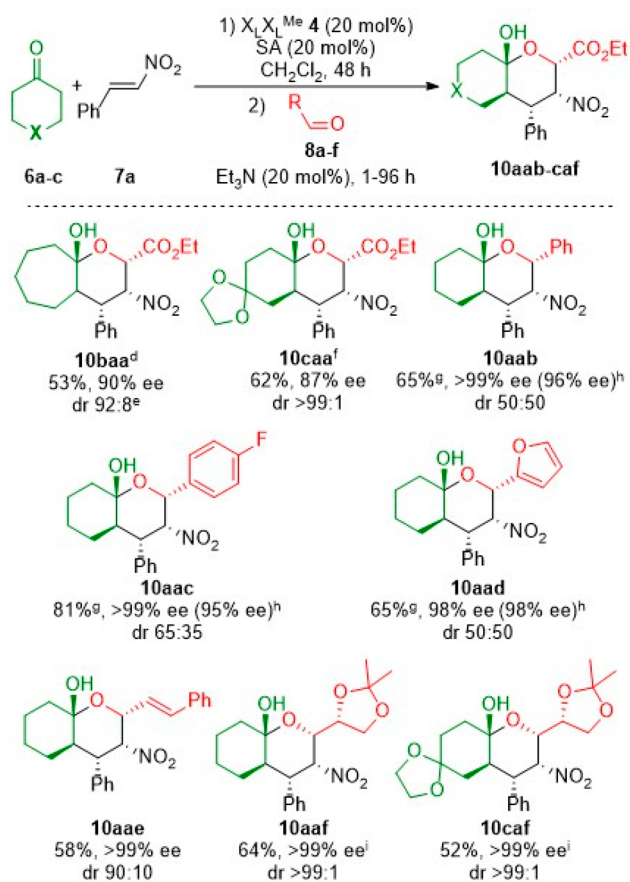46%, 95% ee
dr >99:1

10aia[f,h]
55%, 99% ee
dr >99:1

[a]The first step was conducted using ketone **6a** (1.0 mmol) and the corresponding *trans*-β-nitroalkene **7a–i** (1.1 mmol) in the presence of 10 mol % O₂N-X_L-X_L^{Me}-OMe **4** and 20 mol % salicylic acid, at room temperature for 48 h. The second step was conducted using aldehyde **8a** (2.0 mmol) and 20 mol % Et₃N and monitored by ¹H NMR until the starting materials were totally consumed (>99% conversion). [b]Yields refer to isolated products. [c]ee determined by HPLC with a chiral stationary phase corresponding to major enantiomer (2*S*,3*R*,4*S*,4a*R*,8a*S*)-**10aaa−aia**. [d]The Michael reaction required 3 days. [e]Performed in toluene. [f]The second step was performed at 0 °C. [g]The product was obtained as an inseparable mixture of diastereomers. [h]The Michael reaction required 6 days.

were used as starting materials, no formation of the corresponding Michael adducts was observed in the presence of salicylic acid or TFA. In contrast, when cyclopentanone **6f** was employed, the final tetrahydropyran derivative could not be isolated due low conversion and selectivity (see the Supporting Information).

The Henry reaction step was found to be compatible with aromatic and aliphatic conjugated aldehydes (Scheme 2).

Scheme 2. Enantioselective Michael–Henry–Hemiketalization Reaction with Different Ketones 6 and Aldehydes 8[a–c]

10baa[d]
53%, 90% ee
dr 92:8[e]

10caa[f]
62%, 87% ee
dr >99:1

10aab
65%[g], >99% ee (96% ee)[h]
dr 50:50

10aac
81%[g], >99% ee (95% ee)[h]
dr 65:35

10aad
65%[g], 98% ee (98% ee)[h]
dr 50:50

10aae
58%, >99% ee
dr 90:10

10aaf
64%, >99% ee[i]
dr >99:1

10caf
52%, >99% ee[i]
dr >99:1

[a]The first step was conducted using the corresponding ketone 6a–c (1.0 mmol) and trans-β-nitrostyrene 7a (1.1 mmol) in the presence of 10 mol % O₂N-X_L-X_L^Me-OMe 4 and 20 mol % salicylic acid, at room temperature for 48 h. The second step was conducted using the corresponding aldehyde 8a–f (2.0 mmol) and 20 mol % Et₃N and monitored by ¹H NMR until the starting materials were totally consumed (>99% conversion). [b]Yields refer to isolated products. [c]Enantiomeric excesses determined by HPLC with a chiral stationary phase corresponding to major enantiomer (2S,3R,4S,4aR,8aS)-10aab–caf. [d]The first step was performed with trifluoroacetic acid as an additive, and the second step was conducted using 1 equiv of Et₃N. The product was obtained as an inseparable mixture of diastereomers. [e]Diastereomeric ratio related to the cyclization of syn- and anti-Michael adducts. [f]The first step required 7 days. [g]Yields refer to the sum of both diastereomers. [h]ee refers to (2S,3S,4S,4aR,8aS)-10aab'–caf' enantiomers. [i]ee refers to de (diastereomeric excess) measured by ¹H NMR.

Because the studied aldehydes were less electrophilic than model ethyl glyoxylate 8a, in some cases changes in the number of equivalents of the aldehyde and triethylamine were required (see the Supporting Information for further details). The reaction could be applied to a broad scope of aldehydes to generate the corresponding THP derivatives in good overall yields and excellent enantioselectivities. Nevertheless, the diasteroselectivity of the process fluctuated from low to excellent depending on the aldehyde employed. Heteroaromatic aldehydes such as furfural could also be applied to this one-pot reaction with 1 equiv of triethylamine. The final products were obtained as a 50:50 mixture of diastereomers, in

good overall yield and excellent enantioselectivities. Because problems arose in the purification of the final products, isomerization of 10aad into 10aad' was investigated (vide infra). This method was extended to chiral aldehyde 8f aldehyde, which would act as a chiral auxiliary leading to the formation of a single diastereomer. Indeed, final product 10aaf was obtained in good yield and excellent diastereo- and enantioselectivity. Finally, cyclohexanone 6a was replaced by 1,4-cyclohexanedione monoethylene acetal 6c to generate the more complex THP derivative 10caf in moderate yield and with virtually complete stereocontrol.

The isomerization of final products 10aad and 10aad' (see also entries 9 and 10, respectively, of Table 1) was studied. Treatment with DBU (1 equiv) at room temperature for 16 h led to 10aad' quantitatively (Scheme 3a). This reaction was

Scheme 3. (a) Isomerization Reaction for the Formation of Derivative 10aad' and (b) One-Pot Synthesis of Compound 10aad' with 1 equiv of DBU
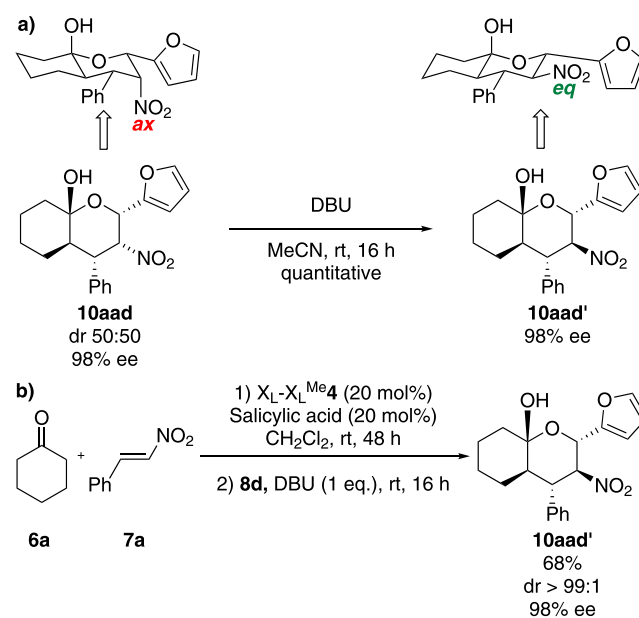
successfully scaled up to 1 mmol without losing the reaction efficiency. Hence, in the one-pot process for the straight synthesis of epimer 10aad', the second step was conducted using 1 equiv of DBU. Under these conditions, the desired product was obtained in good yield with excellent diastereo- and enantiocontrol (Scheme 3b).

This isomerization is compatible with the change in configuration of the carbon atom contiguous to the nitro group, which passes from an axial position in 10aad to a thermodynamically favored equatorial geometry in 10aad' (see Scheme 3 and the Supporting Information for additional DFT calculations).

In summary, in this study, we have found that one-pot Michael–Henry–hemiketalization reaction of ketones catalyzed by dimeric γ-peptides 3–5 leads to bicyclic densely substituted octahydro-2H-chromene derivatives with up to five chiral centers in good yields and excellent distereo- and enantioselectivities. This one-pot process constitutes an example of distinct catalytic properties on passing from monomeric to condensed dimeric species.

D

ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c01230.

General experimental procedures, NMR spectra for all compounds and full characterization of the described products, and computational data, including energies, harmonic analysis, and Cartesian coordinates, of all relevant stationary points (PDF)

Accession Codes

CCDC 2090677 and 2090834 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Authors

María de Gracia Retamosa − *Instituto de Síntesis Orgánica y Departamento de Química Orgánica, Universidad de Alicante, 03080 Alicante, Spain; Centro de Innovación en Química Avanzada (ORFEO-CINQA)*, https://orfeocinqa.es/; *Donostia International Physics Center (DIPC), 20018 Donostia-San Sebastián, Spain;* Email: gracia.retamosa@ua.es

Fernando P. Cossío − *Departamento de Química Orgánica I, University of the Basque Country (UPV/EHU), 20018 Donostia-San Sebastián, Spain; Centro de Innovación en Química Avanzada (ORFEO-CINQA)*, https://orfeocinqa.es/; *Donostia International Physics Center (DIPC), 20018 Donostia-San Sebastián, Spain;* Email: fp.cossio@ehu.es

Authors

Maddalen Agirre − *Departamento de Química Orgánica I, University of the Basque Country (UPV/EHU), 20018 Donostia-San Sebastián, Spain; CIC Energigune, Parque Tecnológico de Álava, 01510 Vitoria-Gasteiz, Spain*

Tamara Bello − *Departamento de Química Orgánica I, University of the Basque Country (UPV/EHU), 20018 Donostia-San Sebastián, Spain; Quimatryx Ltd., 2009 Donostia-San Sebastián, Spain*

Jinxiu Zhou − *Departamento de Química Orgánica I, University of the Basque Country (UPV/EHU), 20018 Donostia-San Sebastián, Spain; Department of Polymer Science and Technology, Institute of Polymer Materials, University of the Basque Country (UPV/EHU), 20018 Donostia-San Sebastián, Spain*

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.joc.2c01230

Author Contributions

▽M.A. and T.B. contributed equally to this work.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

REFERENCES

(1) Wang, F.; Dong, Z.-J.; Liu, J-K. Z. Benzopyran-4-one Derivatives from the FungusGanodermaapplanatum. *Z. Naturforsch., B* **2007**, *62*, 1329−1332.

(2) Cutler, H. G.; Cutler, S. J.; Ross, S. A.; Sayed, K. E.; Dugan, F. M.; Bartlett, M. G.; Hill, A. A.; Hill, R. A.; Parker, S. R. Koninginin G, a New Metabolite from Trichoderma aureoviride. *J. Nat. Prod.* **1999**, *62*, 137−139.

(3) D'Souza, A. M.; Paknikar, S. K.; Dev, V.; Beauchamp, P. S.; Kamat, S. P. Biogenetic-Type Synthesis of (+)-Cymbodiacetal, a Constituent of Cymbopogon martinii. *J. Nat. Prod.* **2004**, *67*, 700−702.

(4) Uroos, M.; Lewis, W.; Blake, A. J.; Hayes, C. J. Total Synthesis of (+)-Cymbodiacetal: A Re-evaluation of the Biomimetic Route. *J. Org. Chem.* **2010**, *75*, 8465−8470.

(5) Tu, W.-C.; Wang, S.-Y.; Chien, S.-C.; Lin, F.-M.; Chen, L.-R.; Chiu, C.-Y.; Hsiao, P.-W. Diterpenes from Cryptomeria japonica Inhibit Androgen Receptor Transcriptional Activity in Prostate Cancer Cells. *Planta Medica* **2007**, *73*, 1407−1409.

(6) Clarke, P. A.; Santos, S. Strategies for the Formation of Tetrahydropyran Rings in the Synthesis of Natural Products. *Eur. J. Org. Chem.* **2006**, *2006*, 2045−2053.

(7) Boivin, T. L. B. Synthetic routes to tetrahydrofuran, tetrahydropyran, and spiroketal units of polyether antibiotics and a survey of spiroketals of other natural products. *Tetrahedron* **1987**, *43*, 3309−3362.

(8) Vetica, F.; Chauhan, P.; Dochain, S.; Enders, D. Asymmetric organocatalytic methods for the synthesis of tetrahydropyrans and their application in total synthesis. *Chem. Soc. Rev.* **2017**, *46*, 1661−1674.

(9) Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Córdova, A. Direct Amino Acid Catalyzed Asymmetric Synthesis of Polyketide Sugars. *Angew. Chem., Int. Ed.* **2005**, *44*, 1343−1345.

(10) Hahn, R.; Raabe, G.; Enders, D. Asymmetric Synthesis of Highly Functionalized Tetrahydropyrans via a One-Pot Organo-catalytic Michael/Henry/Ketalization Sequence. *Org. Lett.* **2014**, *16*, 3636−3639.

(11) Chandrasekhar, S.; Mallikarjun, K.; Pavankumarreddy, G.; Rao, K. V.; Jagadeesh, B. Enantiopure cycloalkane fused tetrahydropyrans through domino Michael-ketalizations with organocatalysis. *Chem. Commun.* **2009**, 4985−4987.

(12) Ishikawa, H.; Sawano, S.; Yasui, Y.; Shibata, Y.; Hayashi, Y. Asymmetric One-Pot Four-Component Coupling Reaction: Synthesis of Substituted Tetrahydropyrans Catalyzed by Diphenylprolinol Silyl Ether. *Angew. Chem., Int. Ed.* **2011**, *50*, 3774−3779.

(13) Gurubrahamam, R.; Cheng, Y.-S.; Chen, K. Control of Five Contiguous Stereogenic Centers in an Organocatalytic Kinetic Resolution via Michael/Acetalization Sequence: Synthesis of Fully Substituted Tetrahydropyranols. *Org. Lett.* **2015**, *17*, 430−433.

(14) Despite excellent studies using oligopeptides as organocatalysts for conjugate additions that have been reported, these systems have not been applied to the organocatalyzed synthesis of THPs. See, for example: (a) Schnitzer, T.; Budinská, A.; Wennemers, H. Organo-catalysed conjugate addition reactions of aldehydes to nitroolefins with anti selectivity. *Nat. Catal.* **2020**, *3*, 143−147. (b) Bächle, F.; Duschmalé, J.; Ebner, C.; Pfaltz, A.; Wennemers, H. Organocatalytic asymmetric conjugate addition of aldehydes to nitroolefins: identification of catalytic intermediates and the stereoselectivity-determining step by ESI-MS. *Angew. Chem., Int. Ed.* **2013**, *52*, 12619−

12623. (c) Duschmalé, J.; Wahl, J.; Wiesner, M.; Wennemers, H. Effects of internal and external carboxylic acids on the reaction pathway of organocatalytic 1,4-addition reactions between aldehydes and nitroolefins. *Chem. Sci.* **2013**, *4*, 1312−1318.

(15) Conde, E.; Bello, T.; de Cózar, A.; Sánchez, M.; Vázquez, M. A.; Cossío, F. P. *Chem. Sci.* **2012**, *3*, 1486−1491.

(16) de Gracia Retamosa, M.; de Cózar, A.; Sánchez, M.; Miranda, J. I.; Sansano, J. M.; Castelló, L. M.; Nájera, C.; Jiménez, A. I.; Sayago, F. J.; Cativiela, C.; Cossío, F. P. Remote Substituent Effects on the Stereoselectivity and Organocatalytic Activity of Densely Substituted Unnatural Proline Esters in Aldol Reactions. *Eur. J. Org. Chem.* **2015**, *2015*, 2503−2516.

(17) de Gracia Retamosa, M.; Ruiz-Olalla, A.; Bello, T.; de Cózar, A.; Cossío, F. P. A Three-Component Enantioselective Cyclization Reaction Catalyzed by an Unnatural Amino Acid Derivative. *Angew. Chem., Int. Ed.* **2018**, *57*, 668−672.

(18) Ruiz-Olalla, A.; Retamosa, M. G.; Cossío, F. P. Densely Substituted l-Proline Esters as Catalysts for Asymmetric Michael Additions of Ketones to Nitroalkenes. *J. Org. Chem.* **2015**, *80*, 5588−5599.

(19) Gracia Retamosa, M.; Ruiz-Olalla, A.; Agirre, M.; de Cózar, A.; Bello, T.; Cossío, F. P. Additive and Emergent Catalytic Properties of Dimeric Unnatural Amino Acid Derivatives: Aldol and Conjugate Additions. *Chem. - Eur. J.* **2021**, *27*, 15671−15687.

(20) Burés, J.; Armstrong, A.; Blackmond, D. *J. Am. Chem. Soc.* **2011**, *133*, 8822−8825.