JOC The Journal of Organic Chemistry

Note

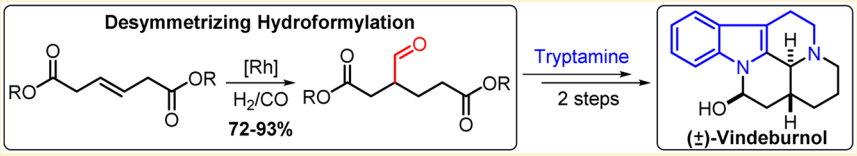
pubs.acs.org/joc

Desymmetrizing Hydroformylation of Dihydromuconic Acid Diesters: Application to the Synthesis of (±)-Vindeburnol

Laura Salacz, Cyrille Charpentier, Jean Suffert, and Nicolas Girard*

Laboratoire d'Innovation Thérapeutique, UMR7200 CNRS/Université de Strasbourg, Faculté de Pharmacie, 74 route du Rhin, 67412 Illkirch, France

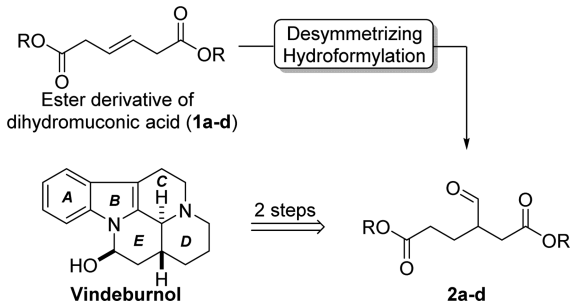
Supporting Information



ABSTRACT: The desymmetrizing hydroformylation of internal alkenes derived from dihydromuconic acid is described. The study of this reaction afforded easy access to polyfunction aldehydes. After the evaluation of the reactivity of the dimethyl ester derivative with various primary amines, this methodology was used to design a rapid synthesis of (±)-vindeburnol from tryptamine in only two steps.

Hydroformylation is one of the most important reactions in the field of homogeneous catalysis. It allows the introduction of an aldehyde function from an olefin with homologation of the carbon chain. This reaction, extensively used in industry,[1] has many advantages: (1) it uses inexpensive reagents (alkene, H_2, CO), (2) it is a robust catalytic system (Co, Rh), (3) it is atom-economic, and (4) it is tolerant of other functions present on the olefin. As a result, many synthetic strategies use this reaction as the key step.[2] Among these tactics, desymmetrizing hydroformylation seems to be particularly attractive in order to design new and efficient routes for the synthesis of natural products. However, to date, it has been underused in total synthesis. Besides the work developed by Breit et al.[3] on the desymmetrizing hydroformylation of dialkenylcarbinols (terminal double bonds), few examples of the desymmetrizing hydroformylation of internal double bonds have been described. What is known includes the following: the hydroformylation of symmetric bicyclic hydrazines for the synthesis of prostaglandin endoperoxide analogues,[4,5] the synthesis of perhydrofuro[2,3-*b*]furans and perhydrofuro[2,3-*b*]pyrans by hydroformylation of *α*,*ω*-alkenediols,[6] the hydroformylation applied to 1,4-diacetoxy-2-butenes for the synthesis of vitamin A[7,8] based on both BASF[9] and Hoffmann-La Roche[10] processes, and work on the desymmetrizing hydroformylation of cyclopropenes[11] and cyclopentenes.[12] In this paper, a desymmetrizing hydroformylation of internal double bonds of dihydromuconic acid diesters is described (Scheme 1). The aldehyde resulting from this reaction, related to those developed in the pioneering work of Harley-Mason,[13] was then used as the precursor for the total synthesis of vindeburnol,[14] an eburnamine vincamine-type synthetic alkaloid that features a pentacyclic core with a D/E ring junction in a *trans* relationship and is a racemic mixture of the diastereoisomer in Scheme 1. Moreover, vindeburnol displays a central vasodilator effect which is now in clinical development against treatment-resistant

Scheme 1. Synthesis of (±)-Vindeburnol Based on Desymmetrizing Hydroformylation



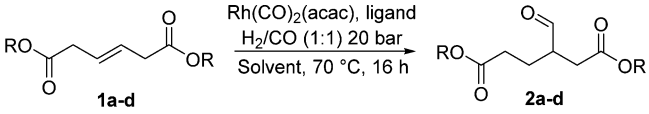
depression under the name BC19.[15] The synthetic strategy developed here allowed the design of the direct synthesis of this molecule in only two steps from tryptamine.[16] First, the most effective hydroformylation conditions were determined, and then the formed aldehyde was subjected to various primary amines to study its reactivity. Finally, the use of tryptamine as a trinucleophile permitted synthesis of (±)-vindeburnol.

Although the olefin derivatives of but-3-enoic acid have shown the appropriate behavior in the course of the hydroformylation reaction with a low formation of isomerized and reduced compounds,[17] it could be anticipated that dihydromuconic acid derivatives could be easily isomerized to give mainly a hex-2-enedioate moiety. Initially, the hydroformylation of commercially available dimethyl (*E*)-hex-3-enedioate (**1a**) was studied using [$Rh(CO)_2(acac)$] as the rhodium source (2 mol %) and a monodentate (8 mol %) or bidentate (4 mol %) ligand under 20 bar of syngas at 70 °C for 16 h (Table 1). Surprisingly, the triphenylphosphine ligand

Received: December 7, 2016
Published: January 26, 2017

DOI: 10.1021/acs.joc.6b02939
J. Org. Chem. 2017, 82, 2257−2262

Table 1. Hydroformylation of Dialkyl (*E*)-Hex-3-enedioates 1a−d



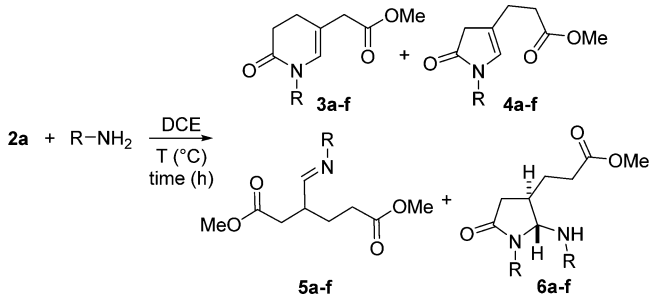
entry	R	ligand	solvent	conv (%)[a]	2/red.[b]/isom[c] ratio[a]
1	Me (**a**)	$P(Ph)_3$	THF	95	100/3/0
2		$P(o\text{-tolyl})_3$	THF	95	100/24/43
3		dppf	THF	95	100/16/11
4		$P(OPh)_3$	THF	100	100/6/0
5		Xantphos	THF	100	100/36/0
6		*rac*-BINAP	THF	100	100/34/0
7		$P(OPh)_3$	toluene	100	100/4/0
8		$P(OPh)_3$	DCE	100	100/6/0
9		$P(OPh)_3$	DCM	100	100/6/0
10		$P(OPh)_3$	ACN	100	100/6/0
11	Et (**b**)	$P(OPh)_3$	THF	100	100/14/0
12	^{i}Pr (**c**)	$P(OPh)_3$	THF	100	100/11/0
13	CF_3CH_2 (**d**)	$P(OPh)_3$	THF	100	100/12/0

[a]Determined by ^{1}H NMR analysis of the crude reaction mixtures. [b]$RO_2C(CH_2)_4CO_2R$. [c]$RO_2CCH{=}CH(CH_2)_2CO_2R$.

efficiently yielded the desired aldehyde with very few reduced compounds and without traces of isomerized product (entry 1). With $P(o\text{-tolyl})_3$ and dppf ligands, the conversion was 95% (entries 2 and 3). However, these last two ligands gave a greater amount of both isomerized and reduced compounds. The best ligand was the triphenyl phosphite, allowing a total conversion of the olefin with a small amount of byproduct (entry 4). Both Xantphos and *rac*-BINAP gave a greater amount of reduced product (entries 5 end 6). Several solvents were tested with triphenyl phosphite ligand, and in all cases, the reaction gave results similar to those achieved in THF (entries 7−10). To evaluate the electronic and steric hindrance effects of the ester moieties during the reaction, various diesters (R= Et, *i*-Pr, and CF_3CH_2) were synthesized. All of these olefins formed corresponding aldehydes with a complete conversion with only a slight increase in the amount of reduced product (entries 11−13). These results show that ester moieties did not have a major impact on either the conversion and the formation of the isomerized and reduced byproducts. Hence, after purification, aldehydes **2a−d** were obtained in good to very good yields (**2a**, 93%; **2b**, 72%; **2c**, 88%; **2d**, 88%).

In order to synthesize vindeburnol, the condensation of aldehyde **2a** was studied with primary amines to form the 6-membered D ring (Table 2). During this reaction, intermediate imine **5** can cyclize either via a 6-*exo-trig* process to give the desired compound **3** or by a 5-*exo-trig* mechanism to lead to product **4**. To simplify the analysis of crude reaction mixtures, this study was performed with benzylamine as the nucleophile. After, aldehyde **2a** was subjected to benzylamine at 90 °C for 30 min in a sealed tube. The ^{1}H NMR analysis of the crude reaction mixture showed the presence of four compounds: cyclized products **3a** and **4a** in a 10/1 ratio and a large quantity of the imine **5a** and the cyclic compound **6a**, obtained by a double condensation of the benzylamine (entry 1). The mono- and bidimensional NMR analysis indicated that the latter was a 5- or 6-membered cyclic aminal with a *trans* configuration between the side carbon chain and the benzylamine moiety. To consume all of the imine, the reaction temperature (entries 2−4) was increased. Thus, only cyclic products formed at 150 °C. However, the **3a**/**4a** ratio was altered to 2.3/1. Moreover, increasing the reaction time (to 3 h) at 90 °C led to the complete cyclization of the imine and the **3a**/**4a** ratio remained unchanged (entry 5). If increasing the reaction temperature promotes product **4a**, decreasing it can promote the desired compound **3a** (entries 6 and 7). Indeed, at 21 °C, the **3a**/**4a** ratio grew to 49/1, but at the same time, the aminal **6a** became the main reaction product. Therefore, performing the reaction between 90 and 110 °C (entries 8 and 9) was the most efficient set of conditions for inducing the formation of product **3a**. By conducting the reaction at 110 °C for 16 h, the **3a**/**4a** ratio was 5.7/1 with 70% of isolated yield in **3a**.

Table 2. Study of the Condensation of Aldehyde 2a with Primary Amines



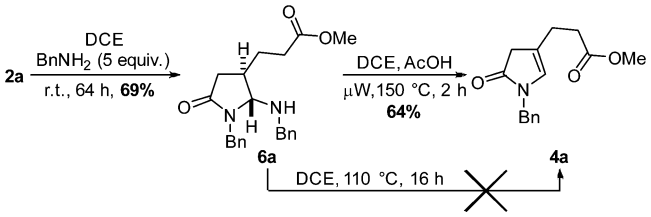
entry	R	*T* (°C)	time (h)	3/4/5/6[a]	yield 3/4[b] (%)
1	$PhCH_2-$ (**a**)	90	0.5	100/9/74/11	
2		110[c]	0.5	100/19/17/8	
3		130[c]	0.5	100/25/10/6	
4		150[c]	0.5	100/37/1/0	
5		90	3	100/10/0/11	
6		70	16	100/8/0/35	
7		21	64	100/2/0/108	
8		90	16	100/11/0/14	43/7
9		110	16	100/15/0/8	70/14
10	2-pyridyl-$(CH_2)_2-$ (**b**)	110	16	100/19/0/13	78/21
11	$MeOCH_2CH_2-$ (**c**)	110	16	100/20/0/17	65/12
12	cyclohexyl-CH_2- (**d**)	110	16	100/27/0/14	68/23
13	cyclopentyl- (**e**)	110	16	100/37/0/3	57/24
14	*α*-methylbenzyl- (**f**)	110	16	87/100/0/0	36/39

[a]Ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures. [b]Isolated yields. [c]Heating under microwave irradiations.

To assign the structure of the cyclic aminal (i.e., 5- or 6-membered ring) and to determine if it is an intermediate of the formation of compounds **3a** and/or **4a**, the reaction was performed at room temperature with 5 equiv of benzylamine (Scheme 2). After 64 h of reaction, the almost exclusively formed cyclic compound was **6a**. It was obtained in 69% yield. To determine if **6a** could be transformed into **3a** and/or **4a** during the course of the reaction, it was subjected to a temperature of 110 °C in DCE for 16 h. Under these conditions **6a** remained stable. However, at 150 °C, and in the presence of AcOH (1.1 equiv), **6a** was transformed into **4a** by elimination of the benzylamine moiety. Therefore, **6a** is the 5-membered cyclic aminal. Moreover, to check if **6a** could be obtained from **4a**, the latter was subjected to 5 equiv of

DOI: 10.1021/acs.joc.6b02939
J. Org. Chem. 2017, 82, 2257−2262

Scheme 2. Formation and Reactivity of Cyclic Aminal 6a

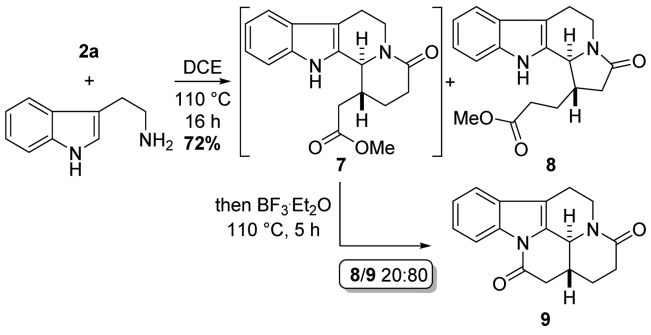


benzylamine in DCE at 110 °C, but after 16 h of reaction only the starting material was recovered.

All of these results show that the ratio **3a**/**4a**/**6a** is dependent upon the reaction temperature. Indeed, at room temperature, the rate of cyclization of imine becomes similar to that of the formation of acyclic aminal. Then, the latter cyclizes, exclusively, via a 5-*exo*-*trig* process to give **6**. On one hand, when the reaction temperature is increased, the cyclization rate of the imine increases faster than that of the formation of acyclic aminal. On the other hand, when the reaction temperature becomes too high, the **3**/**4** ratio decreases. The most appropriate set of conditions for the formation of **4** (110 °C, 16 h) was tested on various primary amines (Table 2, entries 10−14). In the case of α-secondary amines (entries 10−12), the **3**/**4** ratio and the yield of **3** are equivalent to those obtained with benzylamine. However, regarding α-tertiary amines (entries 13 and 14), the **3**/**4** ratio decreases, and in the case of α-methylbenzylamine it reverses. These results show, in addition to temperature, that steric hindrance of the amine plays a crucial role on the **3**/**4** ratio.

With tryptamine as nucleophile (Scheme 3), the intermediate iminium ions spontaneously undergo a diastereoselective

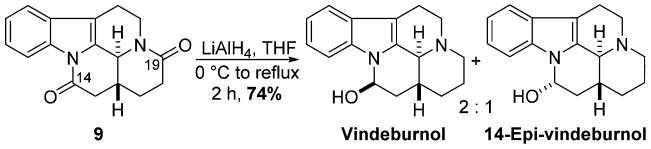
Scheme 3. Tandem Synthesis of Diamide 9



Pictet−Spengler reaction under the reaction conditions to give indoloquinolizidine[18] (**7**) and harmicine[19] (**8**) derivatives. Moreover, the last cyclization which allowed the formation of the desired diamide **9** already began. However, to drive this reaction to completion, the addition of a catalytic amount of acid ($BF_3{\cdot}Et_2O$, 20 mol %) was required. Thus, the pentacylic core of vindeburnol was obtained by a tandem reaction from two simple substrates, aldehyde **2a** and tryptamine. The **7**/**8** ratio, which is directly related to the regioselectivity of the first cyclization, shows that tryptamine has the same behavior as benzylamine. It should be noted that, if the acid is introduced at the beginning of the reaction, the harmicine type compound **9** becomes the main product (**8**/**9**: 55/45). Moreover, compounds **8** and **9** are easily separable on silica gel chromatography.

To achieve the synthesis of vindeburnol, the last reduction step must allow the complete reduction of the carbonyl group in position 19 and partial reduction of that carbonyl group in position 14 (Scheme 4).[20] This is possible because their

Scheme 4. Synthesis of Vindeburnol



reactivity is different. The carbonyl group in position 14 has a ketone-like reactivity, whereas the one in position 19 behaves as an amide function. Indeed, when the diamide **9** is subjected to LAH in refluxing THF for 2 h, two diastereoisomers are obtained, namely vindeburnol and the 14-*epi*-vindeburnol in a 2/1 ratio, in a good yield (74%), after overnight treatment at room temperature of the reaction mixture with an aqueous solution of sodium hydroxide at 2 M.[21] As the hemiaminal in vindeburnol is a stereochemically labile, the observed diastereoisomeric ratio is dependent upon the pH of the reaction. 14-*epi*-Vindeburnol can be epimerized in vindeburnol under acidic[22] or basic[14] conditions.

In conclusion, a new desymmetrizing hydroformylation of dihydromuconic acid derivatives has been developed. The study of the reactivity, with respect to primary amines of the obtained aldehyde, allowed the design of an efficient two-step synthesis of (±)-vindeburnol from tryptamine. Currently, the development of an asymmetric version of this reaction is under investigation, and the application of this methodology to the synthesis of vinca-type alkaloids is in progress.

EXPERIMENTAL SECTION

General Information. Reagents were obtained from commercial sources and used without any further purification. Thin-layer chromatography was performed on silica gel 60F254 plates. Hydroformylation reactions were performed in a stainless steel benchtop autoclave equipped with a gas addition kit. NMR spectra were recorded at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Conditions are specified for each spectrum (temperature 25 °C unless specified). Chemical shifts are reported in parts per million (ppm) relative to residual solvent, and coupling constants (*J*) are reported in hertz (Hz). Signals are described as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintuplet), sextet (sextuplet), sept (septuplet), m (multiplet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dddd (doublet of doublet of doublet of doublets), dt (doublet of triplets), ddt (doublet of doublet of triplets), qt (quartet of doublets), br s (broad singlet), br d (broad doublet), br q (broad quadruplet), br t (broad triplet), and br dd (broad doublet of doublets). HRMS were recorded at 70 eV by electrospray ionization with time-of-flight analyzer (ESI-TOF). Melting points were determined in open capillary tubes and are uncorrected.

General Procedure for the Synthesis of Diesters 1a−d. To the specified solvent (50 mL) under argon was slowly added thionyl chloride (4 eq, 55.51 mmol, 4 mL) at −10 °C and the mixture stirred for 15 min. (*E*)-Hex-3-enedioic acid (1 equiv, 2.00 g, 13.88 mmol) was then added portion wise, and the mixture was allowed to reach its reaction temperature and stirred overnight. The mixture was then concentrated under vacuum and dissolved in 30 mL of CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$ (3 × 20 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by silica gel liquid chromatography (eluent: pentane/EtOAc).

*Dimethyl (E)-Hex-3-enedioate (**1a**).*[23] Solvent: methanol. Reaction temperature: rt. Chromatography eluent: 80/20−50/50. Yield: 96%

DOI: 10.1021/acs.joc.6b02939
J. Org. Chem. 2017, 82, 2257−2262

(2.29 g, 13.32 mmol) of a colorless oil. R_f: 0.53 (30% EtOAc in pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.70−5.68 (m, 2H), 3.68 (s, 6H), 3.10 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 126.0, 51.9, 37.8.

*Diethyl (E)-Hex-3-enedioate (**1b**).*[23] Solvent: ethanol. Reaction temperature: rt. Chromatography eluent: 80/20. Yield: 92% (2.56 g, 12.77 mmol) of a colorless oil. R_f: 0.54 (20% EtOAc in pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.70 (m, 2H), 4.14 (q, J = 7.1 Hz, 4H), 3.08 (m, 4H), 1.26 (t, J = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 126.1, 60.8, 38.1, 14.3.

*Diisopropyl (E)-Hex-3-enedioate (**1c**).*[24] Solvent: propan-2-ol. Reaction temperature: reflux. Chromatography eluent: 85/15−80/20. Yield: 97% (3.07 g, 13.46 mmol) of an orangish solid. R_f: 0.67 (20% EtOAc in pentane). Mp: <50 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.67 (m, 2H), 4.99 (sept, J = 6.2 Hz, 2H), 3.03 (m, 4H), 1.22 (s, 6H), 1.21 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 126.0, 68.1, 38.3, 21.9.

*Bis(2,2,2-trifluoroethyl) (E)-Hex-3-enedioate (**1d**).* Solvent: trifluoroethanol. Reaction temperature: reflux. Chromatography eluent: 85/15−80/20. Yield: 84% (3.59 g, 11.66 mmol) of a white powder. R_f: 0.24 (5% EtOAc in pentane). Mp: <50 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74 (m, 2H), 4.48 (q, J = 8.4 Hz, 4H), 3.22 (m, 42bH). ^{19}F NMR (400 MHz, $CDCl_3$): δ −73.9 (t, J = 8.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 125.8, 123.0 (q, J = 276.3 Hz), 60.6 (q, J = 36.7 Hz), 37.1. HRMS (ESI-TOF): calcd for $[C_{10}H_{10}F_6O_4 + Na]^+$ 331.0381, found 331.03715 (Δ = 1.3).

General Procedure for the Synthesis of Aldehydes 2a−d. A solution of $Rh(CO)_2(acac)$ (0.02 equiv) and $P(OPh)_3$ (0.08 equiv) in anhydrous THF (2 mL), prepared in a Schlenk glassware under an argon atmosphere, was introduced under argon into a stainless steel autoclave containing the substrate (**1a−d**) (1 equiv) in anhydrous THF to reach a final concentration of 0.2 M. The reactor was purged three times with H_2/CO (1:1, 5 bar) and filled with H_2/CO (1:1, 20 bar). The reactor was heated to 70 °C and stirred for 16 h. The reactor was then cooled to ambient temperature and vented to ambient pressure. The reaction mixture was evaporated, and the residue was purified by column chromatography on silica gel.

*Dimethyl 3-Formylhexanedioate (**2a**).* Hydroformylation was performed following the general procedure starting from **1a** (200 mg, 1.161 mmol). Purification on silica gel eluting with 30−50% EtOAc in pentane afforded the title compound as a colorless oil (218 mg, 1.078 mmol, 93%). R_f: 0.25 (30% EtOAc in pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (s, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 2.87 (quint, J = 6.5 Hz, 1H), 2.74 (dd, J = 16.6, 7.9 Hz, 1H), 2.49−2.38 (m, 3H) 2.11 (sextet, J = 7.2 Hz, 1H), 1.83 (sextet, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.0, 173.1, 172.0, 52.1, 51.9, 46.9, 32.9, 31.1, 23.6. HRMS (ESI-TOF): calcd for $[C_9H_{14}O_5 + Na]^+$ 225.0739, found 225.07273 (Δ = 3.0).

*Diethyl 3-Formylhexanedioate (**2b**).* Hydroformylation was performed following the general procedure starting from **1b** (1.00 g, 4.99 mmol). Purification on silica gel eluting with 30−40% EtOAc in pentane afforded the title compound as a colorless oil (830 mg, 3.605 mmol, 72%). R_f: 0.45 (30% EtOAc in pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (s, 1H), 4.15 (m, 4H), 2.86 (quint, J = 6.6 Hz, 1H), 2.72 (dd, J = 16.7, 7.6 Hz, 1H), 2.48−2.36 (m, 3H), 2.10 (sextet, J = 7.2 Hz, 1H), 1.83 (sextet, J = 7.2 Hz, 1H), 1.26 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.1, 172.7, 171.6, 61.0, 60.8, 47.0, 33.2, 31.4, 23.6, 14.3, 14.2. HRMS (ESI-TOF): calcd for $[C_{11}H_{18}O_5 + Na]^+$ 253.1052, found 253.10397 (Δ = 2.9).

*Diisopropyl 3-Formylhexanedioate (**2c**).* Hydroformylation was performed following the general procedure starting from **1c** (500 mg, 2.19 mmol). Purification on silica gel eluting with 5−10% EtOAc in pentane afforded the title compound as a colorless oil (498 mg, 1.928 mmol, 88%). R_f: 0.29 (15% EtOAc in pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (s, 1H), 5.02 (sept, J = 6.2 Hz, 2H), 2.85 (quint, J = 6.7 Hz, 1H), 2.69 (dd, J = 16.5, 7.7 Hz, 1H), 2.43 (dd, J = 16.5, 5.5 Hz, 1H), 2.36 (m, 2H), 2.09 (sextet, J = 7.3 Hz, 1H), 1.81 (sextet, J = 7.3 Hz, 1H), 1.24 (s, 6H), 1.23 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.1, 172.1, 171.0, 68.4, 68.0, 47.0, 33.5, 31.7, 23.6, 21.8, 21.7. HRMS (ESI-TOF): calcd for $[C_{13}H_{22}O_5 + Na]^+$ 281.1365, found 281.1366 (Δ = 2.6).

*Bis(2,2,2-trifluoroethyl) 3-Formylhexanedioate (**2d**).* Hydroformylation was performed following the general procedure starting from **1d** (342 mg, 1.11 mmol). Purification on silica gel eluting with 5−20% EtOAc in pentane afforded the title compound as a colorless oil (330 mg, 0.976 mmol, 88%). R_f: 0.24 (20% EtOAc in pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (d, J = 0.5 Hz, 1H), 4.57−4.41 (m, 4H), 2.93 (m, 1H), 2.86 (m, 1H), 2.59−2.52 (m, 3H), 2.18 (sextet, J = 7.2 Hz, 1H), 1.89 (m, 1H). ^{19}F NMR (400 MHz, $CDCl_3$): δ −73.8 (q, J = 8.3 Hz), −73.9 (q, J = 8.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.0, 171.0, 170.0, 122.8 (q, J = 277.3 Hz), 122.7 (q, J = 276.9 Hz), 60.6 (q, J = 36.8 Hz), 60.5 (q, J = 36.6 Hz), 46.6, 32.4, 30.7, 23.2. HRMS (ESI-TOF): calcd for $[C_{11}H_{12}F_6O_5 + Na]^+$ 361.0487, found 361.0482 (Δ = 0.2).

General Procedure for the Synthesis of Enamides 3a−f and 4a−f. To a solution of dimethyl 3-formylhexanedioate **2a** (0.50 mmol, 1 equiv) in DCE (10 mL) under argon in a sealed tube was added the amine (1.1 equiv). The reaction mixture was stirred during 16 h at 110 °C. Then the solution was concentrated under reduced pressure, and the residue containing a mixture of compounds **3** and **4** was purified by column chromatography on silica gel.

With benzylamine as amine:

*Methyl 2-(1-Benzyl-6-oxo-1,4,5,6-tetrahydropyridin-3-yl)acetate (**3a**).* Purification on silica gel eluting with 50−0% pentane in EtOAc afforded the title compound as a yellowish oil (91 mg, 0.35 mmol, 70%). R_f: 0.56 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.22 (m, 5H), 5.94 (m, 1H), 4.68 (s, 2H), 3.68 (s, 3H), 3.01 (s, 2H), 2.63 (m, 2H), 2.38 (t, J = 7.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 169.0, 137.2, 128.8, 127.8, 127.6, 127.5, 112.8, 52.1, 49.0, 39.0, 31.2, 24.4. HRMS (ESI-TOF): calcd for $[C_{15}H_{17}NO_3 + H]^+$ 260.1287, found 260.12847 (Δ = 0.1).

*Methyl 3-(1-Benzyl-5-oxo-4,5-dihydro-1H-pyrrol-3-yl)propanoate (**4a**).* Purification on silica gel eluting with 50−0% pentane in EtOAc afforded the title compound as a colorless oil (18 mg, 0.07 mmol, 14%). R_f: 0.30 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.22 (m, 5H), 5.91 (m, 1H), 4.60 (s, 2H), 3.77 (br s, 2H), 3.68 (s, 3H), 2.66−2.55 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 171.6, 157.9, 137.4, 128.9, 128.1, 127.7, 122.2, 54.2, 52.0, 46.0, 31.9, 24.8. HRMS (ESI-TOF): calcd for $[C_{15}H_{17}NO_3 + H]^+$ 260.1287, found 260.12809 (Δ = 0.1).

With 2-(2-aminoethyl)pyridine as amine:

*Methyl 2-(6-Oxo-1-(2-(pyridin-2-yl)ethyl)-1,4,5,6-tetrahydropyridin-3-yl)acetate (**3b**).* Purification on silica gel eluting with 0−10% MeOH in AcOEt afforded the title compound as a orangish oil (107 mg, 0.39 mmol, 78%). R_f: 0.26 (5% MeOH in EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (m, 1H), 7.55 (td, J = 7.7, 1.8 Hz, 1H), 7.13 (br d, 7.9 Hz, 1H), 7.09 (m, 1H), 5.80 (m, 1H), 3.79 (br t, J = 7.4 Hz, 2H), 3.64 (s, 3H), 2.99 (br t, J = 7.4 Hz, 2H), 2.91 (s, 2H), 2.46 (br t, J = 8.1 Hz, 2H), 2.25 (t, J = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 169.0, 158.6, 149.3, 136.5, 128.3, 123.7, 121.6, 111.9, 51.9, 46.5, 38.3, 37.0, 31.2, 24.2. HRMS (ESI-TOF): calcd for $[C_{15}H_{18}N_2O_3 + H]^+$ 275.1396, found 275.13883 (Δ = 0.7).

*Methyl 3-(1-Benzyl-5-oxo-4,5-dihydro-1H-pyrrol-3-yl)propanoate (**4b**).* Purification on silica gel eluting with 0−10% MeOH in EtOAc afforded the title compound as a yellowish oil (29 mg, 0.105 mmol, 21%). R_f: 0.10 (5% MeOH in EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (br s, 1H), 7.59 (br t, J = 7.5 Hz, 1H), 7.18 (br d, J = 7.8 Hz, 1H), 7.13 (m, 1H), 5.79 (br s, 1H), 3.80 (br t, J = 7.1 Hz, 2H), 3.75 (s, 2H), 3.66 (s, 3H), 3.04 (br t, J = 7.1 Hz, 2H), 2.62−2.50 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 171.6, 158.9, 157.6, 149.2, 136.9, 123.6, 122.4, 121.8, 55.1, 52.0, 41.9, 37.2, 31.9, 24.7. HRMS (ESI-TOF): calcd for $[C_{15}H_{18}N_2O_3 + H]^+$ 275.1396, found 275.13989 (Δ = 3.2).

With 2-methoxyethylamine as amine:

*Methyl 2-(1-(2-Methoxyethyl)-6-oxo-1,4,5,6-tetrahydropyridin-3-yl)acetate (**3c**).* Purification on silica gel eluting with 0−10% MeOH in EtOAc afforded the title compound as a colorless oil (74 mg, 0.325 mmol, 65%). R_f: 0.48 (5% MeOH in EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.04 (m, 1H), 3.69 (s, 3H), 3.62 (t, J = 5.5 Hz, 2H), 3.50 (t,

DOI: 10.1021/acs.joc.6b02939
J. Org. Chem. 2017, 82, 2257−2262

J = 5.5 Hz, 2H), 3.33 (s, 3H), 3.04 (br s, 2H), 2.54 (m, 2H), 2.33 (br t, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 170.0, 129.0, 111.5, 71.2, 59.0, 52.0, 46.2, 39.0, 31.2, 24.2. HRMS (ESI-TOF): calcd for $[C_{11}H_{17}NO_4 + H]^+$ 228.1236, found 228.12313 (Δ = 0.4).

*Methyl 3-(1-(2-Methoxyethyl)-5-oxo-4,5-dihydro-1H-pyrrol-3-yl)-propanoate (**4c**).* Purification on silica gel eluting with 0−10% MeOH in EtOAc afforded the title compound as a colorless oil (14 mg, 0.06 mmol, 12%). R_f: 0.24 (5% MeOH in EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83 (m, 1H), 4.00 (d, J = 1.2 Hz, 2H), 3.67 (s, 3H), 3.56 (br t, J = 5.2 Hz, 2H), 3.50 (m, 2H), 3.31 (s, 3H), 2.66 (m, 2H), 2.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 171.6, 158.1, 122.1, 71.8, 58.8, 56.2, 52.0, 41.9, 31.9, 24.7. HRMS (ESI-TOF): calcd for $[C_{11}H_{17}NO_4 + H]^+$ 228.1236, found 228.12292 (Δ = 0.5).

With cyclohexanemethylamine as amine:

*Methyl 2-(1-(Cyclohexylmethyl)-6-oxo-1,4,5,6-tetrahydropyridin-3-yl)acetate (**3d**).* Purification on silica gel eluting with EtOAc afforded the title compound as a colorless oil (89 mg, 0.34 mmol, 68%). R_f: 0.61 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.91 (m, 1H), 3.70 (s, 3H), 3.27 (d, J = 7.2 Hz, 2H), 3.05 (d, J = 0.6 Hz, 2H), 2.54 (m, 2H), 2.33 (br t, J = 8.0 Hz, 2H), 1.74−1.55 (m, 6H), 1.25−1.11 (m, 3H), 0.96−0.87 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 169.0, 128.8, 111.6, 52.5, 52.1, 39.0, 37.3, 31.3, 30.8, 26.5, 25.9, 24.4. HRMS (ESI-TOF): calcd for $[C_{15}H_{23}NO_3 + H]^+$ 266.1756, found 266.17541 (Δ = 1.3).

*Methyl 3-(1-(Cyclohexylmethyl)-5-oxo-4,5-dihydro-1H-pyrrol-3-yl)propanoate (**4d**).* Purification on silica gel eluting with EtOAc afforded the title compound as a colorless oil (30 mg, 0.115 mmol, 23%). R_f: 0.30 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83 (m, 1H), 3.87 (s, 2H), 3.68 (br s, 3H), 3.21 (br d, J = 7.2 Hz, 2H), 2.66 (m, 2H), 2.59 (m, 2H), 1.70 (m, 2H), 1.61 (m, 4H), 1.17 (m, 3H), 0.94 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 171.8, 157.1, 122.5, 55.5, 52.0, 48.5, 37.4, 32.0, 30.9, 26.5, 25.9, 24.7. HRMS (ESI-TOF): calcd for $[C_{15}H_{23}NO_3 + H]^+$ 266.1756, found 266.17531 (Δ = 0.9).

With cyclopentylamine as amine:

*Methyl 2-(1-Cyclopentyl-6-oxo-1,4,5,6-tetrahydropyridin-3-yl)-acetate (**3e**).* Purification on silica gel eluting with 70−0% pentane in EtOAc afforded the title compound as a colorless oil (68 mg, 0.286 mmol, 57%). R_f: 0.55 (30% pentane in EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.99 (s, 1H), 4.98 (quint, J = 8.5 Hz, 1H), 3.71 (s, 3H), 3.08 (s, 2H), 2.54 (t, J = 8.0 Hz, 2H), 2.31 (t, J = 8.0 Hz, 2H), 1.89 (m, 2H), 1.70 (m, 2H), 1.61 (m, 2H), 1.47 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 168.8, 123.7, 113.0, 53.1, 52.1, 39.4, 31.7, 30.0, 24.6, 24.0. HRMS (ESI-TOF): calcd for $[C_{13}H_{19}NO_3 + H]^+$ 238.1443, found 238.14385 (Δ = 0.4).

*Methyl 3-(1-Cyclopentyl-5-oxo-4,5-dihydro-1H-pyrrol-3-yl)-propanoate (**4e**).* Purification on silica gel eluting with 70−0% pentane in EtOAc afforded the title compound as a colorless oil (28 mg, 0.12 mmol, 24%). R_f: 0.24 (30% pentane in EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 (br s, 1H), 4.49 (quint, J = 8.1 Hz, 1H), 3.84 (s, 2H), 3.68 (s, 3H), 2.67 (m, 2H), 2.59 (m, 2H), 1.90 (m, 2H), 1.69 (m, 2H), 1.61 (m, 2H), 1.48 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 171.6, 157.0, 122.6, 52.4, 52.0, 51.0, 32.0, 30.3, 24.8, 24.0. HRMS (ESI-TOF): calcd for $[C_{13}H_{19}NO_3 + H]^+$ 238.1443, found 238.14425 (Δ = 2.0).

With (±)-α-methylbenzylamine as amine:

*Methyl 2-(6-Oxo-1-(1-phenylethyl)-1,4,5,6-tetrahydropyridin-3-yl)acetate (**3f**).* Purification on silica gel eluting with 75−0% pentane in EtOAc afforded the title compound as a colorless oil (49 mg, 0.18 mmol, 36%). R_f: 0.60 (30% pentane in EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.25 (m, 5H), 6.00 (q, J = 7.0 Hz, 1H), 5.77 (s, 1H), 3.64 (s, 3H), 2.96 (s, 2H), 2.60 (t, J = 8.1 Hz, 2H), 2.33 (m, 2H), 1.52 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 168.7, 140.6, 128.7, 127.5, 127.2, 123.7, 113.1, 52.0, 49.6, 39.2, 31.7, 24.0, 17.6. HRMS (ESI-TOF): calcd. for $[C_{16}H_{19}NO_3 + H]^+$ 274.1443, found 274.14385 (Δ = 0.3).

*Methyl 3-(5-Oxo-1-(1-phenylethyl)-4,5-dihydro-1H-pyrrol-3-yl)-propanoate (**4f**).* Purification on silica gel eluting with 75−0% pentane in EtOAc afforded the title compound as a colorless oil (53 mg, 0.195 mmol, 39%). R_f: 0.27 (30% pentane in EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.21 (m, 5H), 5.83 (s, 1H), 5.51 (q, J = 7.1 Hz, 1H), 3.81 (d, J = 18.9 Hz, 1H), 3.64 (s, 3H), 3.48 (d, J = 18.9 Hz, 1H), 2.62−2.51 (m, 4H), 1.56 (d, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 171.2, 157.7, 141.1, 128.7, 127.5, 127.0, 122.2, 52.0, 50.5, 48.9, 31.9, 24.8, 17.7. HRMS (ESI-TOF): calcd for $[C_{16}H_{19}NO_3 + H]^+$ 274.1443, found 274.14288 (Δ = 3.3).

With tryptamine as amine: After the solution was heated at 110 °C during 16 h, $BF_3{\cdot}Et_2O$ (0.2 equiv) was added, and the solution was stirred to reflux during 5 h. A saturated aqueous solution of $NaHCO_3$ (20 mL) was added, and the mixture was extracted with DCM (2 × 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel eluting with 0−10% MeOH in EtOAc.

*trans-Methyl 3-(3-Oxo-2,3,5,6,11,11b-hexahydro-1H-indolizino-[8,7-b]indol-1-yl)propanoate (**8**).* Purification afforded the title compound as an orangish powder (22 mg, 0.07 mmol, 14%). R_f: 0.43 (5% MeOH in AcOEt). Mp: 63−64 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.91 (br s, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.42 (d, J = 7.7 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 4.58 (d, J = 6.3 Hz, 1H), 4.53 (m, 1H), 3.75 (s, 3H), 3.02 (m, 1H), 2.91−2.78 (m, 2H), 2.67 (q, J = 7.4 Hz, 1H), 2.62−2.45 (m, 2H), 2.37−2.24 (m, 3H), 1.99 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 172.2, 136.7, 133.0, 126.9, 122.4, 119.9, 118.4, 111.4, 108.6, 59.6, 52.3, 38.5, 38.1, 37.7, 31.8, 29.7, 21.1. HRMS (ESI-TOF): calcd for $[C_{18}H_{20}N_2O_3 + H]^+$ 313.1552, found 313.15443 (Δ = 0.8).

*trans-1,2,5,6,13,13a-Hexahydro-3H-indolo[3,2,1-de]pyrido [3,2,1-ij][1,5]naphthyridine-3,12(4^{1}H)-dione (**9**).* Purification afforded the title compound as a orangish powder (81 mg, 0.29 mmol, 58%). R_f: 0.25 (5% MeOH in AcOEt). Mp: 168−169 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (m, 1H), 7.46 (m, 1H), 7.34 (m, 2H), 5.08 (ddd, J = 13.3, 4.5, 2.8 Hz, 1H), 4.27 (dt, J = 11.2, 2.4 Hz, 1H), 3.01 (m, 1H), 2.92 (dd, J = 17.3, 3.6 Hz, 1H), 2.80 (m, 2H), 2.70 (ddt, J = 18.0, 5.9, 1.2 Hz, 1H), 2.66 (dd, J = 17.3, 12.3 Hz, 1H), 2.55 (ddd, J = 18.2, 12.6, 6.9 Hz, 1H), 2.21 (m, 1H), 2.02 (dddd, J = 12.6, 6.6, 3.3, 1.5 Hz, 1H), 1.77 (qd, J = 12.6, 6.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 166.9, 135.4, 132.3, 129.3, 125.2, 124.5, 118.7, 116.3, 112.8, 55.2, 39.1, 38.3, 37.4, 32.3, 26.1, 20.6. HRMS (ESI-TOF): calcd for $[C_{17}H_{16}N_2O_2 + H]^+$ 281.1290, found 281.1287 (Δ = 0.9).

Synthesis of 6a. *trans-Methyl 3-(1-benzyl-2-(benzylamino)-5-oxopyrrolidin-3-yl)propanoate (**6a**).* In a dry 25 mL round-bottom flask was solubilized dimethyl 3-formylhexanedioate **2a** (101 mg, 0.50 mmol, 1 equiv) in DCE (3 mL) under argon, and then benzylamine (273 μL, 2.50 mmol, 5 equiv) was added. The reaction mixture was stirred during 64 h at room temperature. Then the solution was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel eluting with 50−80% EtOAc in pentane to yield 126 mg (69%) of **6a** as a whitish oil. R_f: 0.49 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.25 (m, 10H), 4.97 (d, J = 14.6 Hz, 1H), 4.15 (d, J = 14.6 Hz, 1H), 4.09 (d, J = 4.2 Hz, 1H), 3.75 (d, J = 13.0 Hz, 1H), 3.70 (s, 3H), 3.67 (d, J = 13.0 Hz, 1H), 2.75 (dd, J = 16.9, 8.7 Hz, 1H), 2.35 (m, 2H), 2.22 (m, 1H), 2.13 (dd, J = 16.9, 6.1 Hz, 1H), 1.88 (sextet, J = 7.0 Hz, 1H), 1.72 (br s, 1H), 1.66 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 173.3, 139.8, 136.8, 128.9, 128.6, 128.2, 128.0, 127.7, 127.4, 51.8, 47.4, 43.8, 37.3, 36.3, 31.8, 29.3. HRMS (ESI-TOF): calcd for $[2C_{22}H_{26}N_2O_3 + Na]^+$ 755.3785, found 755.37658 (Δ = 1.8).

Synthesis of (±)-Vindeburnol and (±)-14-*epi*-Vindeburnol. To a solution of **9** (244 mg, 0.870 mmol, 1 equiv) in THF (10 mL) at 0 °C under argon was added dropwise a solution of $LiAlH_4$ in THF (2.6 mL, 2.60 mmol, 1 M), and the solution was stirred for 15 min. Then the reaction mixture was warmed to room temperature, stirred for 15 min, and warmed at reflux for 2 h. After the mixture was cooled at room temperature, 20 mL of aqueous solution of NaOH (2 M) was added dropwise, and the mixture was stirred overnight. After extraction with EtOAc (3 × 20 mL) the organic layers were dried over dry Na_2SO_4 and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with 0−10% MeOH in EtOAc to yield (±)-vindeburnol (134 mg, 58%) as a yellowish solid and (±)-14-*epi*-vindeburnol (39 mg, 14%) as a yellowish solid.

DOI: 10.1021/acs.joc.6b02939
J. Org. Chem. 2017, 82, 2257−2262

(±)-(4¹S,12S*,13aR*)-2,3,4¹,5,6,12,13,13a-Octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-12-ol ((±)-Vindeburnol).*[25] R_f: 0.21 (5% MeOH in AcOEt). Mp: 205−206 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.43 (dt, J = 7.8, 0.8 Hz, 1H), 7.35 (d, J = 7.5 Hz, 1H), 7.05 (br t, J = 7.6 Hz, 1H), 7.00 (br t, J = 7.4 Hz, 1H), 6.14 (d, J = 6.9 Hz, 1H), 5.90 (m, 1H), 3.04 (dd, J = 11.3, 5.8 Hz, 1H), 2.95 (m, 1H), 2.77 (m, 1H), 2.64 (m, 2H), 2.41 (td, J = 11.4, 4.4 Hz, 1H), 2.16 (td, J = 11.1, 2.6 Hz, 1H), 1.98−1.89 (m, 3H), 1.78−1.61 (m, 3H), 1.15 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 136.0, 134.3, 128.2, 120.0, 119.2, 117.6, 111.3, 103.7, 73.8, 63.7, 54.6, 52.6, 37.4, 30.8, 29.5, 25.4, 21.2. HRMS-ESI (m/z): calcd for $[C_{17}H_{20}N_2O + H]^+$ 269.1654, found 269.16419 (Δ = 2.4).

(±)-(4¹S,12S*,13aR*)- 2,3,4¹,5,6,12,13,13a-Octahydro-1H-indolo[3,2,1-de]pyrido[3,2,1-ij][1,5]naphthyridin-12-ol ((±)-14-epi-Vindeburnol).*[25] R_f: 0.14 (5% MeOH in AcOEt). Mp: 201−202 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.65 (m, 1H), 7.37 (m, 1H), 7.03 (m, 2H), 6.44 (d, J = 9.0 Hz, 1H), 5.51 (td, J = 9.0, 5.7 Hz, 1H), 3.02 (dd, J = 11.2, 5.6 Hz, 1H), 2.92 (dt, J = 11.0, 2.7 Hz, 1H), 2.79−2.61 (m, 3H), 2.45 (td, J = 11.2, 4.4 Hz, 1H), 2.20 (m, 2H), 1.77−1.55 (m, 4H), 1.44 (m, 1H), 1.17 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 137.4, 135.4, 127.9, 120.3, 119.3, 117.6, 111.9, 103.9, 77.8, 63.2, 54.3, 52.0, 38.8, 36.0, 29.6, 25.2, 21.3. HRMS-ESI (m/z): calcd for $[C_{17}H_{20}N_2O + H]^+$ 269.1654, found 269.16467 (Δ = 0.6).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02939.

^{1}H and ^{13}C NMR spectra of all synthesized compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: nicolas.girard@unistra.fr.

ORCID

Nicolas Girard: 0000-0003-4610-9872

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Centre National de la Recherche Scientifique and the University of Strasbourg (Unistra). We are grateful to Patrick Wehrung, Barbara Schaeffer, and Pauline Meyer for the mass spectroscopy experiments (Service Commun d'Analyse, Unistra). We are also grateful to Dr. Morgan Donnard (School of Pharmacy) and Daniel Schwartz (Institute of Technology) from the University of Strasbourg for fruitful discussions.

■ DEDICATION

This paper is dedicated to Dr. André Mann for his important contributions in the field of hydroformylation reaction in organic synthesis.

■ REFERENCES

(1) Franke, R.; Selent, D.; Börner, A. *Chem. Rev.* **2012**, *112*, 5675−5732.

(2) (a) Anton-Torrecillas, C.; Loza, M. I.; Brea, J.; Gonzalez-Gomez, J. C. *Org. Biomol. Chem.* **2016**, *14*, 2264−2271. (b) Chauhan, P. S.; Sacher, J. R.; Weinreb, S. M. *Org. Lett.* **2015**, *17*, 806−808. (c) Risi, R. M.; Maza, A. M.; Burke, S. D. *J. Org. Chem.* **2015**, *80*, 204−216.

(3) (a) Breit, B.; Breuninger, D. *J. Am. Chem. Soc.* **2004**, *126*, 10244−10245. (b) Breit, B.; Breuninger, D. *Eur. J. Org. Chem.* **2005**, *2005*, 3916−3929. (c) Bigot, A.; Breuninger, D.; Breit, B. *Org. Lett.* **2008**, *10*, 5321−5324. (d) Breit, B.; Bigot, A. *Chem. Commun.* **2008**, *47*, 6498−6500.

(4) Wilson, R. M.; Schnapp, K. A.; Merwin, R. K.; Ranganthan, R.; Moats, D. L.; Conrad, T. T. *J. Org. Chem.* **1986**, *51*, 4028−4035.

(5) Bournaud, C.; Lecourt, T.; Micouin, L.; Méliet, C.; Agbossou-Niedercorn, F. *Eur. J. Org. Chem.* **2008**, *2008*, 2298−2302.

(6) Roggenbuck, R.; Schmidt, A.; Eilbracht, P. *Org. Lett.* **2002**, *4*, 289−291.

(7) Chansarkar, R.; Mukhopadhyay, K.; Kelkar, A. A.; Chaudhari, R. V. *Catal. Today* **2003**, *79−80*, 51−58.

(8) Ünveren, H. H. Y.; Schomäcker, R. *Catal. Lett.* **2005**, *102*, 83−89.

(9) Himmele, W.; Aquila, W. W. US Patent No. 3,661,980, 1972.

(10) Fitton, P.; Moffet, H. US Patent No. 4,124,619, 1978.

(11) Sherrill, W. M.; Rubin, M. *J. Am. Chem. Soc.* **2008**, *130*, 13804−13809.

(12) You, C.; Wei, B.; Li, X.; Yang, Y.; Liu, Y.; Lv, H.; Zhang, X. *Angew. Chem., Int. Ed.* **2016**, *55*, 6511−6514.

(13) (a) Barton, J. E. D.; Harley-Mason, J. *Chem. Commun.* **1965**, 298−299. (b) Harley-Mason, J.; Kaplan, M. *Chem. Commun.* **1967**, *0*, 915−916.

(14) Roussel-Uclaf. US Patent No. 4,291,038, 1981.

(15) Polak, P. E.; Kalinin, S.; Braun, D.; Sharp, A.; Lin, S. X.; Feinstein, D. L. *J. Neurochem.* **2012**, *121*, 206−216.

(16) Previous synthesis of vindeburnol from tryptamine: (a) Sevenet, T. M.; Thal, C.; Husson, H.-P.; Potier, P. FR Patent No. 2190113, 1972. (b) Husson, H.-P.; Imbert, T.; Thal, C.; Potier, P. *Bull. Soc. Chim. Fr.* **1973**, *6*, 2013−2016. (c) Imbert, T.; Thal, C.; Husson, H.-P.; Potier, P. *Bull. Soc. Chim. Fr.* **1973**, *9−10*, 2705−2709. (d) Mondal, P.; Argade, N. P. *Org. Biomol. Chem.* **2016**, *14*, 10394−10406.

(17) (a) Šmejkal, T.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 311−315. (b) Dydio, P.; Dzik, W. I.; Lutz, M.; de Bruin, B.; Reek, J. N. H. *Angew. Chem., Int. Ed.* **2011**, *50*, 396−400. (c) Dydio, P.; Detz, R. J.; Reek, J. N. H. *J. Am. Chem. Soc.* **2013**, *135*, 10817−10828. (d) Yu, Z.; Eno, M. S.; Annis, A. H.; Morken, J. P. *Org. Lett.* **2015**, *17*, 3264−3267.

(18) Jung-Deyon, L.; Giethlen, B.; Mann, A. *Eur. J. Org. Chem.* **2011**, *2011*, 6409−6412.

(19) (a) Chakraborty, I.; Jana, S. *Synthesis* **2013**, *45*, 3325−3331. (b) Lin, J.-B.; Xu, S.-M.; Xie, J.-K.; Li, H.-Y.; Xu, P.-F. *Chem. Commun.* **2015**, *51*, 3596−3599.

(20) Magnus, P.; Brown, P. *J. Chem. Soc., Chem. Commun.* **1985**, *0*, 184−186.

(21) This workup is necessary to cleanly isolated the mixture of two diastereomers.

(22) (a) Lounasmaa, M.; Din Belle, D.; Tolvanen, A. *Heterocycles* **1999**, *51*, 1125−1130. (b) Aktogu, N.; Clemence, F.; Oberlander, C. EP Patent, No. 88402871.3, 1988.

(23) Rajendra, G.; Miller, M. J. *Tetrahedron Lett.* **1987**, *28*, 6257−6260.

(24) Edvinsson, S.; Johansson, S.; Larsson, A. *Tetrahedron Lett.* **2012**, *53*, 6819−6821.

(25) Jokela, R.; Lounasmaa, M. *Tetrahedron* **1989**, *45*, 303−308.

DOI: 10.1021/acs.joc.6b02939
J. Org. Chem. 2017, 82, 2257−2262