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The First Enantioselective Total Synthesis of (−)-*trans*-Dihydronarciclasine

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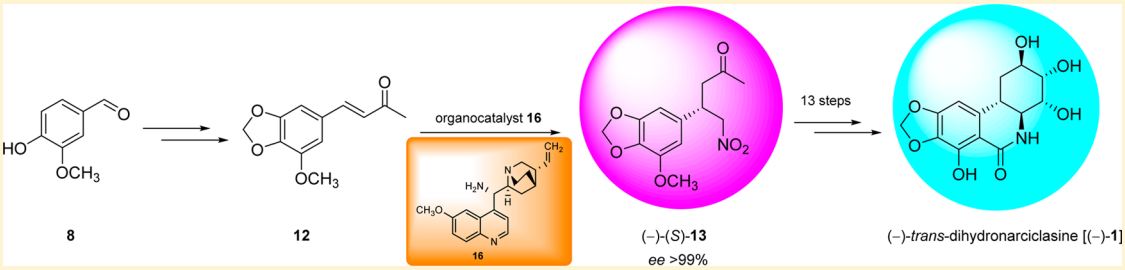
Supporting Information



ABSTRACT: A feasible and enantioselective total synthesis of (−)-*trans*-dihydronarciclasine [(−)-**1**], a highly biologically active alkaloid, was devised starting from vanillin (**8**). The key step of this new synthesis was an asymmetric, organocatalytic Michael addition, in which an optically active nitropentanone [(−)-**13**] was obtained from a butenone derivative (**12**). Excellent enantioselectivity (>99% ee) was achieved using the (8*S*,9*S*)-9-amino(9-deoxy)epiquinine (**16**) organocatalyst. The target molecule can be prepared in 13 steps from compound (−)-**13**. The total synthesis has provided a facile and first access to the *ent*-form of naturally occurring (+)-*trans*-dihydronarciclasine, a highly potent cytostatic alkaloid.

(+)-*trans*-Dihydronarciclasine [(+)-**1**] belongs to the family of natural phenanthridone alkaloids, a subclass of the *Amaryllidaceae* alkaloid family including pancratistatin (**2**), narciclasine (**3**), 7-deoxy-*trans*-dihydronarciclasine (**4**), 7-deoxypancratistatin (**5**), and lycoricidine (**6**) (Figure 1), all possessing potent cytostatic effects and important antiviral activity, respectively.[1−8] Among these phenanthridone alkaloids, (+)-*trans*-dihydronarciclasine has the highest antitumor potency, according to data from the National Cancer Institute (NCI, USA).[9] Furthermore, its antiviral activity against the flaviviruses (e.g., Japanese encephalitis, yellow fever, or Dengue) is also more significant than that of compounds **2**−**6** or commensurate with them.[10] Most recently, its remarkable anti-Zika virus activity has also been reported.[11]

Compound (+)-**1** was first isolated from the bulbs of the white rain lily (*Zephyranthes candida*), a tropical medicinal plant, but in an extremely low yield.[12] Since then, its enantioselective total synthesis has been developed by four groups,[11,13] while that of the racemic alkaloid [(±)-**1**] has been realized by three groups,[14] including ours.[14c] It should be noted that (±)-*trans*-dihydronarciclasine can be obtained by catalytic hydrogenation of the naturally occurring narciclasine (**3**),[15] which was the first isolated member of this subclass, or rather its tetraacetyl derivative after deprotection.[15c] Using these methods, however, the inactive and unwanted *cis*-isomer (**7**) (Figure 2) with other byproducts was also be formed.[15c] Moreover, the purification of (+)-**1** with column chromatography is difficult, resulting in significant loss.[15c,16a,c] This obvious method was performed by some groups[13] long before the first isolation of (+)-**1** from natural sources[12] during the incipient chemical and biological investigation of narciclasine (**3**).[13] Although the extraction of **3** from *Narcissus* species has resulted in a slightly better yield[16] than that of (+)-**1** from *Zephyranthes candida*,[12] this method is, nevertheless, expensive.

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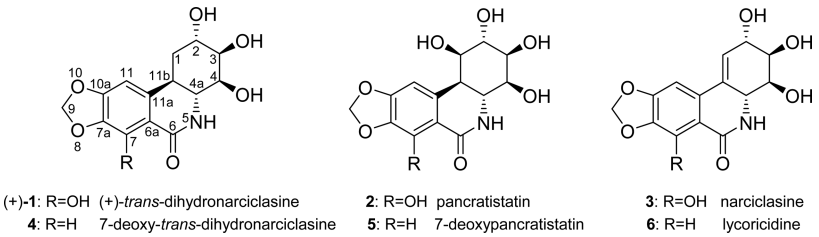

Figure 1. Members of the narciclasine subclass of the natural phenanthridone alkaloids (**1**–**6**).

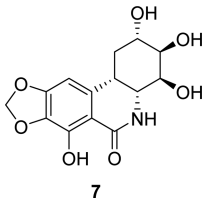

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Figure 2. Structure of *cis*-dihydronarciclasine (**7**).

Surprisingly, almost 50 total syntheses of the less active members of this alkaloid subclass (compounds **2**, **3**, **5**, and **6**) have been reported,[1] but only a few processes (four enantioselective[11,13] and three racemic routes[14]) for that of *trans*-dihydronarciclasine (**1**) have been published. In most of these methods, expensive starting materials were used and the intermediates were almost exclusively isolated by column chromatography. Accordingly, the elaboration of a facile and efficient enatioselective total synthesis for this alkaloid is required to enable further biological studies.

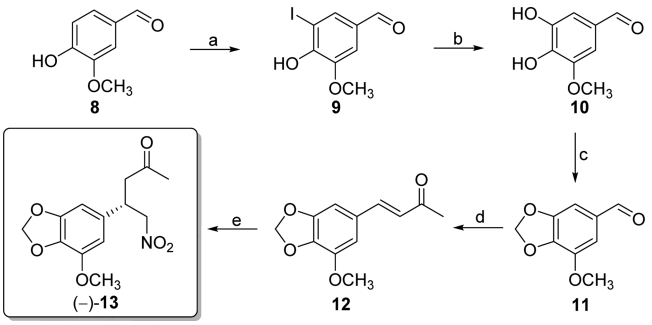
Earlier we reported the stereoselective total synthesis of racemic [(±)-**4**][17a] and the enantioselective method for (−)-7-deoxy-*trans*-dihydronarciclasine [(−)-**4**],[17b] while that of (±)-*trans*-dihydronarciclasine [(±)-**1**] has recently been published as a short paper.[14c] In this work, based partly on our previous experience, we describe the enantioselective total synthesis of compound (−)-**1**, the enantiomer of the title alkaloid. Furthermore, neither harsh conditions nor expensive starting material (vanillin) and reagents are required in most of the steps; that is, this method represents the least expensive access to the title alkaloid.

RESULTS AND DISCUSSION

As shown in Scheme 1, the first step of the total synthesis was iodination of vanillin (**8**). Using a known method,[18] iodovanillin (**9**) was obtained in 99% yield. Compound **9** was hydrolyzed with aqueous NaOH, in the presence of $CuSO_4$;[19] however in our hands this step was accompanied by some dehalogenation. Therefore, the crude product was recrystallized from toluene, removing the dehalogenated byproducts completely, to give compound **10** in 64% yield. Next, myristicin aldehyde (**11**) was produced from the pure dihydroxyaldehyde **10** via a dioxolane ring closure reaction using CH_2Br_2 in dimethylformamide (DMF), in the presence of K_2CO_3 and CuO.[19] The improved workup method, which involved aqueous precipitation of the product instead of extraction, afforded compound **11** in 94% yield. Claisen–Schmidt condensation of **11** with acetone using NaOH smoothly afforded the new butenone derivative **12** in 67% yield after distillation.

In the next step, a conjugate addition of nitromethane to enone **12**, there was an opportunity to accomplish this reaction enantioselectively to give the optically active nitropentanone

Scheme 1. Synthesis of Compound (−)-13[a]



[a]Reagents and conditions: (a) I_2, KI, K_2CO_3, H_2O, rt, 3 h, 99%; (b) 20% NaOH/H_2O, $CuSO_4$, reflux, 16 h, 64%; (c) CH_2Br_2, K_2CO_3, CuO, DMF, 110 °C, 4 h, 94%; (d) acetone, NaOH, H_2O, rt, 20 h, 67% (after distillation); (e) CH_3NO_2, organocatalyst **16**, rt, 7 d, 57%, ee > 99%.

13. At first, we adopted the previous procedure[20] in which the Jørgensen's organocatalyst[21] [(4*S*,2*R*/*S*)-4-benzyl-1-methylimidazolidine-2-carboxylic acid (**14**)] was applied in the enantioselective synthesis of (−)-7-deoxy-*trans*-dihydronarciclasine [(−)-**4**].[17b] However, only moderate enantioselectivity (72% ee) was achieved using this organocatalyst and the (−)-**13** enantiomer was mainly formed (Table 1, entry 1). Moreover, it was isolated in only 37% yield even after a longer reaction time (14 d). Therefore, other asymmetric organocatalysts were tested to obtain higher enantioselectivity.

Turning to the primary amine derivatives of cinchona alkaloids, a cinchonine [(8*R*,9*R*)-9-amino(9-deoxy)-epicinchonine (**15**)] and a quinine derivative [(8*S*,9*S*)-9-amino(9-deoxy)epiquinine (**16**)] were assessed, since they were shown to be highly versatile and efficient enantioselective organocatalysts in several other cases.[22] Moreover, they can readily be synthesized from the commercially available natural compounds cinchonine and quinine, according to the modified procedure of Shaw and co-workers.[23] In a one-pot method compounds **15** and **16** were obtained in 85–87% yields by application of Mitsunobu and Staudinger reactions consecutively. Although the use of (8*R*,9*R*)-9-amino(9-deoxy)-epicinchonine (**15**) as organocatalyst resulted in higher ee (78%) and isolated yield (70%) after 7 d, the opposite enantiomer [(+)-**13**] was formed in excess (Table 1, entry 2). When (8*S*,9*S*)-9-amino(9-deoxy)epiquinine (**16**) was used in this Michael addition, excellent enantioselectivity (>99% ee) in the formation of (−)-**13** (57% isolated yield, Table 1, entry 3) was achieved.

To determine the absolute configuration of the new, enanantiomerically pure nitropentanone derivative (−)-**13**, single-crystal X-ray diffraction measurements were performed. The crystallographic data (Table S1, Supporting Information)

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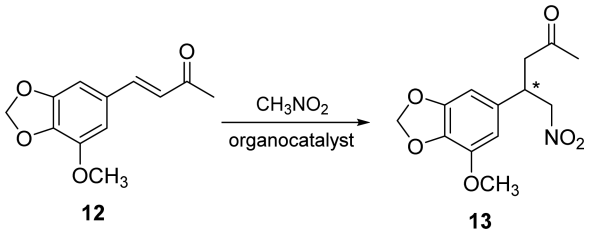
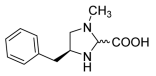
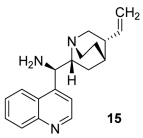
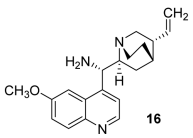
Table 1. Asymmetric Michael Addition Using Organocatalysts (14−16) in the Synthesis of 13[a]



12 13

entry	organocatalyst	reaction time (day)	isolated yield (%)	main enantiomer	ee^b (%)
1	 14	14	37	(−)-**13**	72
2	 15	7	70	(+)-**13**	78
3	 16	7	57	(−)-**13**	>99

[a]Reaction conditions: compound **12** (37 mmol), organocatalyst (20 mol %), nitromethane (30 mL), rt. [b]Determined by chiral HPLC (Figures S83−S85, Supporting Information).

permitted definition of its (10*S*) absolute configuration (Figure 3).

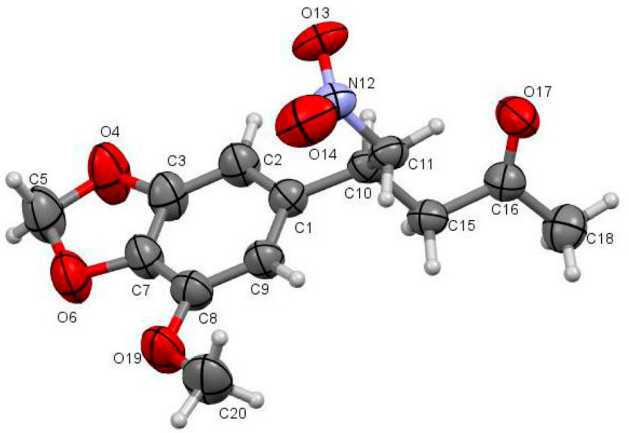


Figure 3. Molecular structure of compound (*S*)-(−)-**13** determined by the single-crystal X-ray diffraction method (ORTEP representation). Displacement ellipsoids are drawn at the 50% probability level.

As seen in Scheme 2, conversion of enantiopure nitropentanone (−)-**13** into hydroxycyclohexanone (−)-**17** was achieved via a Claisen−Henry reaction in moderate yield (38%) after recrystallization from EtOAc. This cyclization resulted in one enantiomer, and it was likely assisted by a hydrogen bond that formed between the nitro and hydroxy groups during the cyclohexane ring closure (Figure 4). The stereoselectivity strongly suggets that the nitro-aldol step occurs last after formation of a 1,3-dicarbonyl intermediate in the Claisen reaction. Similar observations were made by Walker[24] in the synthesis of racemic 3-hydroxy-4-nitro-5-arylcyclohexanones. This strong interaction is evidenced by the significantly shifted peak of the −OH group from 4.09 ppm to 6.02 ppm in the ^{1}H NMR spectrum of compound (−)-**17** compared to those of intermediates (+)-**18** and (−)-**19**. Although compound (+)-**18** also contains $-NO_2$ and −OH groups, the lower chemical shift value (4.09 ppm) suggests that the C-1 spiro group reduces the strength of this hydrogen bond.

Furthermore, the crystallographic data of (−)-**17** obtained by single-crystal X-ray diffraction measurements (Table S2, Supporting Information) also confirmed this structure and facilitated definition of its (3*R*, 4*S*, 5*S*) absolute configuration (Figure 5 and Scheme 2). Since the subsequent chemical transformations have no influence on the configurations of the C-4 and C-5 stereogenic centers, the final product should be the enantiomer of naturally occurring *trans*-dihydronarciclasine, i.e., (−)-**1**.

Protection of hydroxyketone (−)-**17** was carried out using ethylene glycol to give compound (+)-**18**. In this step, due to the potential for dehydration of (−)-**17** with destruction of the C-3 and C-4 stereogenic centers, the dehydration was not done in the usual way (*p*-TsOH, Dean−Stark apparatus), but it was performed with anhydrous oxalic acid at room temperature and in anhydrous MeCN in 90% yield. The nitro group of (+)-**18** was hydrogenated quantitatively to aminoketal (−)-**19** over 10% Pd/C (Selcat Q[25]), in MeOH. This hydrogenation required a temperature of 80 °C most likely due to the strong adsorption of compound (−)-**19** on palladium induced by the tetrasubstituted aromatic moiety.[26] Selective conversion of aminoketal (−)-**19** to urethane (−)-**20** was achieved in a biphasic (THF/H_2O) reaction with methyl chloroformate in 99% yield, while the hydroxy group remained intact. The carbonyl group in compound (−)-**20** was unmasked in acetone containing a stoichiometric amount of *p*-toluenesulfonic acid, but dehydration also took place to afford enone (−)-**21** in

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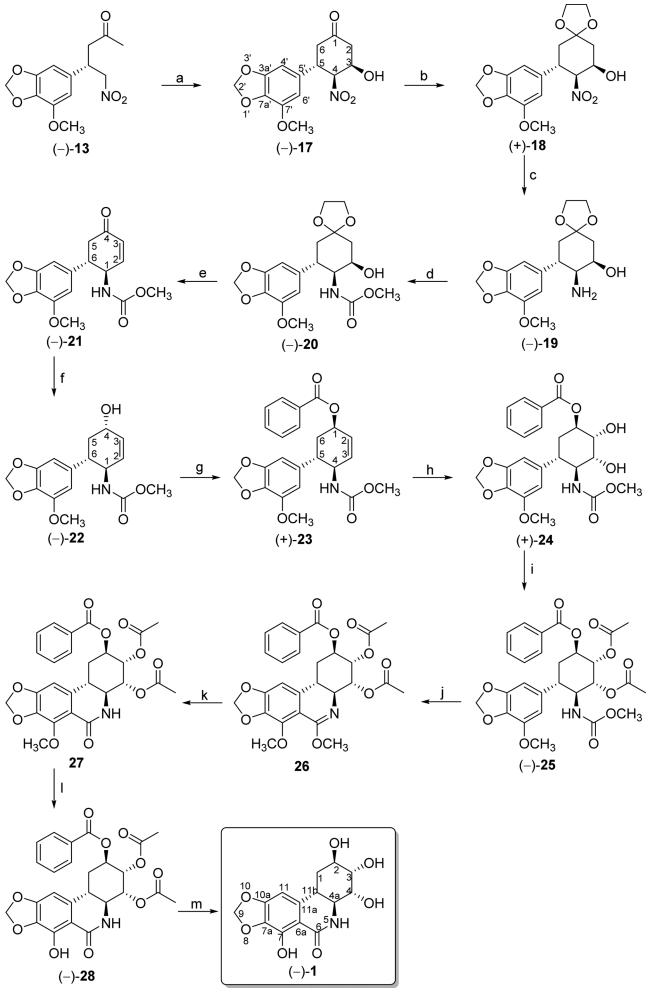
Scheme 2. Synthesis of Compound (−)-1[a]



[a]Reagents and conditions: (a) HCOOEt, $NaOCH_3$, Et_2O, rt, 20 h, 38%, ee 95%; (b) $(CH_2OH)_2$, $(COOH)_2$, CH_3CN, rt, 3 d, 90%, ee 99%; (c) H_2, 10% Pd/C, MeOH, 80 °C, 7 h, quant.; (d) $ClCOOCH_3$, $NaOH/H_2O$, THF, rt, 2 h, 99%, ee 99%; (e) *p*-TsOH, acetone, reflux, 1 h, 99%, ee 93%; (f) $NaBH_4$, $CaCl_2$, CH_3OH, 0 °C, 2 h, 96%, ee 99%; (g) PhCOOH, DEAD, PPh_3, THF, rt, 4 h, 63%, ee 97%; (h) OsO_4, H_2O, THF, Ar atm, rt, 24 h, 99%, ee 95%; (i) AcCl, rt, 24 h, 99%, ee 95%; (j) Tf_2O, DMAP, CH_2Cl_2, 0 °C → rt, 22 h, 99%; (k) (i) 2 M HCl/H_2O, THF, rt, 21 h, (ii) AcCl, rt, 21 h, 99%; (l) TMS-Cl, KI, CH_3CN, 60 °C, 1.5 h, 54%; (m) $NaOCH_3/CH_3OH$, THF, rt, 2 h, 99%, ee 92%.

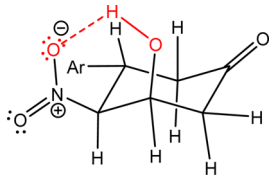


Figure 4. Presumed structure of the hydroxycyclohexanone derivative (−)-**17** and its stabilization by hydrogen bonding.

quantitative yield. To convert it into allylic alcohol (−)-**22**, Utimoto's reduction method ($NaBH_4$, $CaCl_2$)[27] was applied. Compound (−)-**22** was stereoselectively prepared in 96% yield due to the axial attack with a small nucleophile (hydride) derived from $NaBH_4$, which was enhanced by coordination with a calcium ion, resulting in an equatorial position of the

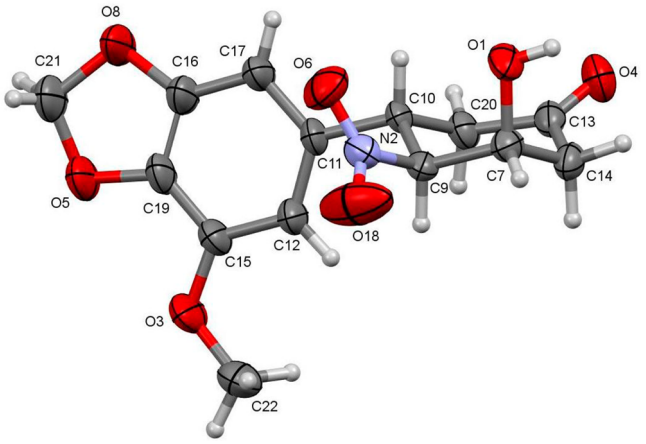


Figure 5. Molecular structure of compound (−)-**17** defined by the single-crystal X-ray diffraction method (ORTEP representation). Displacement ellipsoids are drawn at the 50% probability level.

new, bulky hydroxy group. Since its orientation in the final product is quasi *trans*-axial, it was necessary to invert the C-4 configuration. Accordingly, the conversion of (−)-**22** under Mitsunobu[28] conditions (DEAD, PPh_3, THF), using benzoic acid, afforded benzoate (+)-**23** in 63% yield after column chromatography. Applying the Sharpless−Upjohn method,[29] compound (+)-**23** was converted stereoselectively to the *cis*-diol (+)-**24** in 99% yield using *N*-methylmorpholine *N*-oxide, in the presence of OsO_4 catalyst in THF/H_2O. This *cis*-addition is *anti* to the allylic bulky axial benzoate group, which resulted in the predominant formation of the target product. Protection of the hydroxy groups was achieved with acetyl chloride, giving (−)-**25** in quantitative yield.

Formation of the lactam moiety was performed by applying the Banwell modification[30] of the Bischler−Napieralski reaction. The methoxyphenanthridine intermediate **26** was obtained in 99% yield during this cyclization and was subsequently transformed to the lactam **27** under acidic conditions in 99% yield. The aromatic methoxy group in compound **27** was cleaved by TMS-Cl, in the presence of KI, in MeCN to afford phenanthridone (−)-**28** in moderate yield (54%). Finally, the acyl groups were hydrolyzed using a methanolic solution of NaOMe, in THF, to form the title compound (−)-**1** (99%).

In conclusion, (−)-*trans*-dihydronarciclasine [(−)-**1**)] was efficiently prepared from vanillin (**8**), an inexpensive and readily available starting material, in 18 steps with 2.8% overall yield. In addition, the synthetic potential of this newly developed route was evidenced by the highly enantioselective (>99% ee) organocatalytic nitromethane addition to the butenone derivative **12**, allowing the preparation of compound (*S*)-(−)-**13** and thereby access to the title alkaloid. Further investigations to extend this synthesis method to the enantioselective synthesis of other, potentially antineoplastic phenanthridone alkaloid analogues are also in progress.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were measured on a Büchi 510 apparatus using a certified mercury thermometer (ASTM 2C). Optical rotations were measured on a PerkinElmer 241 polarimeter. The IR spectra were obtained on a PerkinElmer 1600 FT-IR instrument. NMR spectra were recorded on a Bruker AV-300 instrument. HPLC analyses were carried out with a Jasco PU-1580 apparatus equipped with a Jasco UV-1575 detector.

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Elemental analyses were performed on a Vario EL III instrument (Elementar Analysensysteme). Precoated silica plates (Merck 60 F_{254}) were used for analytical TLC and Kieselgel 60 for column cromatography. Single-crystal X-ray diffraction measurement was accomplished at room temperature on a single-source microfocus Cu X-ray sealed tube SuperNova diffractometer (Agilent Technologies) with monochromated Cu Kα radiation (λ = 1.5418 Å) and Eos CCD detector. CCDC 1497270 [(*S*)-(−)-**13**] and CCDC 1536751 [(−)-**17**] contain the supplementary crystallographic data (including structure factors) for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Synthesis. *5-Iodovanillin (**9**).* To a solution of $NaHCO_3$ (22.50 g, 0.27 mol) and KI (45.00 g, 0.32 mol) in water (900 mL) was added vanillin (33.75 g, 0.22 mol) under rigorous stirring. Then I_2 (56.70 g, 0.22 mol) was added in four portions in 30 min. The reaction mixture was stirred for 3 h at room temperature and allowed to stand overnight. The crude product was filtered and washed with a diluted $Na_2S_2O_3$ solution and H_2O to give the product as a light brown powder. It was used without further purification. Yield: 99% (61.39 g, 0.22 mol). Mp: 166 °C (lit. 175 °C,[18] 179−180 °C,[31a,b] 179−182 °C[31c,d]); R_f = 0.37 (*n*-hexane/EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H, CHO), 7.83 (s, 1H, 6-H_{Ar}), 7.45 (s, 1H, 2-H_{Ar}), 6.73 (br s, 1H, OH), 3.97 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 56.8 (OCH_3), 80.7 (5-C_{Ar}), 108.9 (2-C_{Ar}), 131.3 (1-C_{Ar}), 136.4 (6-C_{Ar}), 146.8 (3-C_{Ar}), 151.6 (4-C_{Ar}), 189.8 (CHO).

*5-Hydroxyvanillin (**10**).* A mixture of 5-iodovanillin (**9**) (90.48 g, 0.33 mol), $CuSO_4{\cdot}5H_2O$ (16.24 g, 65.10 mmol), and 20% NaOH solution (1500 mL) was heated to reflux and stirred for 20 h. It was cooled below 10 °C and acidified with concentrated HCl to pH = 2. The mixture was filtered, and the aqueous phase was extracted with EtOAc (4 × 900 mL). The combined organic phase was dried over $MgSO_4$ and evaporated to give the dark gray, crude product. After recrystallization from toluene compound **10** was obtained as pale brown crystals. Yield: 64% (35.26 g, 0.21 mol). Mp: 124−126 °C (lit. 128−131 °C,[18] 132−133 °C,[19a] 128−129 °C[19b]); R_f = 0.19 (*n*-hexane/EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H, CHO), 7.16 (s, 1H, 2/6-H_{Ar}), 7.09 (s, 1H, 6/2-H_{Ar}), 6.11 (br s, 1H, OH), 5.67 (br s, 1H, OH), 3.96 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 56.7 (OCH_3), 103.1 (2-C_{Ar}), 113.3 (6-C_{Ar}), 129.2 (1-C_{Ar}), 138.7 (4-C_{Ar}), 144.2 (5-C_{Ar}), 147.5 (3-C_{Ar}), 191.4 (CHO).

*Myristicin Aldehyde (**11**).* To a solution of 5-hydroxyvanillin (**10**) (20.00 g, 0.12 mol) in DMF (250 mL) were added K_2CO_3 (35.00 g, 0.25 mol), CuO (2.60 g, 0.03 mol), and CH_2Br_2 (10 mL, 24.95 g, 0.14 mol). The reaction mixture was heated to 110 °C and stirred for 4 h. It was allowed to cool to room temperature, and the precipitated solid was filtered. The solution was concentrated *in vacuo*, and the residue was poured into H_2O. The crude product was filtered and dried to give pale gray crystals. It was used without further purification. Yield: 94% (20.10 g, 0.11 mol). Mp: 124 °C (lit. 124−126 °C,[32a] 131 °C,[32b,c] 132−133 °C[20,32d]); R_f = 0.52 (*n*-hexane/EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H, CHO), 7.14 (s, 1H, 4/6-H_{Ar}), 7.05 (s, 1H, 6/4-H_{Ar}), 6.10 (s, 2H, OCH_2O), 3.96 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 56.8 (OCH_3), 102.8 (OCH_2O), 103.8 (4-C_{Ar}), 110.6 (6-C_{Ar}), 132.0 (7a-C_{Ar}), 141.2 (5-C_{Ar}), 144.3 (7-C_{Ar}), 149.6 (3a-C_{Ar}), 190.30 (CHO).

*4-(7-Methoxybenzo[1,3]dioxol-5-yl)but-3-en-2-one (**12**).* A solution of myristicin aldehyde (**11**) (20.35 g, 0.11 mol) in acetone (102 mL) was added into H_2O (47 mL), when the starting material was precipitated in a fine crystalline form. Aqueous NaOH solution (from 1.69 g, 0.04 mol of NaOH, and 7.6 mL of water) and finally water (424 mL) were also added, and the yellow mixture was stirred for 20 h at room temperature and left standing for 2 h. The yellow crude product was filtered, washed with H_2O, and dried. Purification via distillation *in vacuo* gave pale yellow crystals. Yield: 67% (16.74 g, 76.01 mmol). Mp: 74−75 °C, bp: 149−152 °C (0.4 mmHg); R_f = 0.49 (*n*-hexane/EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, 1H, *J* = 16.2 Hz, *CH*=CH), 6.77 (s, 1H, 4/6-H_{Ar}), 6.73 (s, 1H, 6/4-H_{Ar}), 6.57 (d, 1H, *J* = 16.2 Hz, CH=*CH*), 6.03 (s, 2H, OCH_2O), 3.93 (s, 3H, OCH_3), 2.36 (s, 3H, CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.7 ($COCH_3$), 56.8 (OCH_3), 101.7 (4-C_{Ar}), 102.2 (OCH_2O), 109.6 (6-C_{Ar}), 126.0 (=*CH*CO), 129.4 (7a-C_{Ar}), 137.8 (5-C_{Ar}), 143.4 (Ar-*CH*=CH), 144.0 (7-C_{Ar}), 149.6 (3a-C_{Ar}), 198.3 (CO); IR (KBr) 3024, 2848, 1668, 1511, 1327, 1231, 1141, 1101, 974, 813 cm^{-1}; anal. calcd for $C_{12}H_{12}O_4$ (220.22) C, 65.45; H, 5.49; found C, 65.43; H, 5.50.

*(S)-(−)-4-(7-Methoxybenzo[1,3]dioxol-5-yl)-5-nitropentan-2-one [(−)-(**13**)].* Benzalacetone **12** (8.15 g, 0.04 mol) and (8*S*,9*S*)-9-amino(9-deoxy)epiquinine (2.39 g, 7.40 mmol) were dissolved in nitromethane (31 mL) and stirred for 7 d at room temperature. The nitromethane was evaporated, and the residue was crystallized from MeOH to give light yellow crystals. Yield was 57% (5.92 g, 0.02 mol). HPLC conditions: TADDOL AS-H (*n*-hexane/isopropyl alcohol = 8:2, flow rate 2.0 mL min^{-1}, 256 nm, 20 °C), $t_{(-)}$ = 21 min and $t_{(+)}$ = 29 min. Mp: 64−66 °C; $[\alpha]^{22}_D$ = −2.3 (*c* 3, $CHCl_3$), ee > 99%; R_f = 0.40 (*n*-hexane/EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (s, 2H, 4-H_{Ar} and 6-H_{Ar}), 5.94 (s, 2H, OCH_2O), 4.64 (dd, *J* = 12.3 and 6.9 Hz, 1H, HC*H*NO_2), 4.53 (dd, *J* = 12.3 and 7.5 Hz, 1H, *H*CHNO_2), 3.91 (quint, *J* = 7.2 Hz, 1H, *CH*CH_2NO_2), 3.89 (s, 3H, OCH_3), 2.86 (d, 2H, *J* = 6.9, Hz CHCH_2CO), 2.13 (s, 3H, COCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.6 (CH_3CO), 39.4 (Ar-*CH*), 46.5 (CHCH_2CO), 57.0 (OCH_3), 79.8 (CH_2NO_2), 101.2 (4-C_{Ar}), 101.8 (OCH_2O), 107.9 (6-C_{Ar}), 133.4 (7a-C_{Ar}), 135.0 (5-C_{Ar}), 144.0 (7-C_{Ar}), 149.6 (3a-C_{Ar}), 205.5 (CH_3COCH_2); IR (KBr) 3012, 1709, 1635, 1550, 1514, 1455, 1353, 1203, 1136, 1106, 1044 cm^{-1}; anal. calcd for $C_{13}H_{15}NO_6$ (281.26) C, 55.51; H, 5.38; N, 4.98; found C, 55.50; H, 5.40; N, 4.96.

*(3R,4S,5S)-(−)-3-Hydroxy-5-(7-methoxybenzo[1,3]dioxol-5-yl)-4-nitrocyclohexanone [(−)-(**17**)].* Dry NaOMe powder (1.95 g, 0.08 mol) was suspended in anhydrous Et_2O (75 mL); then freshly distilled ethyl formate (9.74 mL, 0.12 mol, 8.98 g) and nitropentanone (−)-**13** (5.76 g, 0.02 mol) were added. The reaction mixture was stirred at room temperature for 20 h, cooled at 0 °C, and quenched with H_2O (41 mL). Phases were separated, and the aqueous layer was acidified to pH = 4 with HOAc, at 0 °C. The precipitated crystals were filtered, washed with H_2O, and dried. Recrystallization from EtOAc gave white crystals. Yield: 38% (2.43 g, 7.86 mmol). HPLC conditions: TADDOL AD-H (*n*-hexane/isopropyl alcohol = 8:2, flow rate 0.8 mL min^{-1}, 256 nm, 20 °C), $t_{(+)}$ = 33 min and $t_{(-)}$ = 41 min. Mp: 200−202 °C; $[\alpha]^{22}_D$ = −47.4 (*c* 0.5, THF), ee 95%; R_f = 0.33 (*n*-hexane/EtOAc = 1:1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.73 (s, 1H, 4′/6′-H_{Ar}), 6.72 (s, 1H, 6′/4′-H_{Ar}) 6.02 (d, *J* = 3.5 Hz, 1H, OH), 5.94 (d, *J* = 2.0 Hz, 2H, OCH_2O), 5.70 (dd, *J* = 12.0 and 2.0 Hz, 1H, 4-H), 4.70−4.67 (m, 1H, 3-H), 3.87 (td, *J* = 13.0 and 4.0 Hz, 1H, 5-H), 3.81 (s, 3H, OCH_3), 3.00 (dd, *J* = 14.5 and 3.0 Hz, 1H, 2-H_β), 2.68 (t, *J* = 14.5 Hz, 1H, 6-H_β), 2.41 (dt, *J* = 14.5 and 2.5 Hz, 1H, 2-H_α), 2.34 (ddd, *J* = 14.5 and 4.5 and 2.0 Hz, 1H, 6-H_α); ^{13}C NMR (75 MHz, DMSO-d_6) δ 39.5 (5-C), 46.6 (2-C), 47.5 (6-C), 56.5 (OCH_3), 69.8 (3-C), 89.5 (4-C), 101.3 (4-C_{Ar}), 101.3 (OCH_2O), 107.5 (6-C_{Ar}), 133.8 (7a-C_{Ar}), 135.4 (5-C_{Ar}), 143.3 (7-C_{Ar}), 148.6 (3a-C_{Ar}), 206.3 (1-C); IR (KBr) 3505, 2902, 1636, 1546, 1455, 1328, 1132, 1081 cm^{-1}; anal. calcd for $C_{14}H_{15}NO_7$ (309.27) C, 54.37; H, 4.89; N, 4.53; found C, 54.36; H, 4.90; N, 4.52.

*(3R,4S,5S)-(+)-3-Hydroxy-5-(7-methoxybenzo[1,3]dioxol-5-yl)-4-nitrocyclohexanone Ethylene Acetal [(+)-(**18**)].* To a solution of anhydrous oxalic acid (6.47 g, 0.07 mol) in anhydrous MeCN (109 mL) were added ethylene glycol (18.5 mL, 20.48 g, 0.33 mol) and nitrocyclohexanolone (−)-**17** (2.38 g, 7.70 mmol). The reaction mixture was stirred at room temperature for 3 d and poured into a saturated $NaHCO_3$ solution (305 mL) at 0 °C. The precipitated crystals were filtered, washed with H_2O, and dried. Yield: 90% (2.45 g, 6.93 mmol). HPLC conditions: TADDOL AD-H (*n*-hexane/isopropyl alcohol = 8:2, flow rate 2.0 mL min^{-1}, 256 nm, 20 °C), $t_{(+)}$ = 21 min and $t_{(-)}$ = 40 min. Mp: 141−143 °C; $[\alpha]^{22}_D$ = +13.8 (*c* 1, THF), ee 99%; R_f = 0.81 ($CHCl_3$/acetone = 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (s, 2H, 4′-H_{Ar} and 6′-H_{Ar}), 5.93 (s, 2H, OCH_2O), 4.70 (dd, *J* = 12.0 and 2.7 Hz, 1H, 4-H), 4.63 (dq, *J* = 10.2 and 2.7 Hz, 1H, 3-H), 4.09−3.99 (m, 5H, OCH_2CH_2O and OH), 3.89 (s, 3H, OCH_3), 3.79 (td, *J* = 12.9 and 3.9 Hz, 1H, 5-H), 2.19 (dt, *J* = 14.4 and 2.7 Hz, 1H, 2-H_α), 2.07−1.98 (m, 2H, 2-H_β and 6-H_α), 1.80 (t, *J* = 13.5 Hz, 1H, 6-H_β); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.7 (2-C), 38.7 (5-C), 41.8 (6-

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C), 56.9 (OCH_3), 64.7 (OCH_2CH_2O), 65.4 (OCH_2CH_2O), 69.8 (3-C), 91.3 (4-C), 101.3 (4-C_{Ar}), 101.7 (OCH_2O), 107.8 (6-C_{Ar}), 107.8 (1-C), 132.9 (7a-C_{Ar}), 134.3 (5-C_{Ar}), 143.9 (7-C_{Ar}), 149.4 (3a-C_{Ar}); IR (KBr) 3506, 2902, 1636, 1455, 1329, 1131, 1081 cm^{-1}; anal. calcd for $C_{16}H_{19}NO_8$ (353.32) C, 54.39; H, 5.42; N, 3.96; found C, 54.38; H, 5.44; N, 3.94.

*(3R,4S,5S)-(−)-4-Amino-5-(7-methoxybenzo[1,3]dioxol-5-yl)-cyclohexan-3-ol Ethylene Acetal [(−)-(**19**)].* Over 10% Pd/C catalyst (Selcat Q, 0.67 g) nitroketal (+)-**18** (2.24 g, 6.34 mmol) was hydrogenated in MeOH (60 mL), in a 250 mL stainless steel autoclave equipped with a magnetic stirrer (stirring speed: 1100 rpm). The reduction was carried out at 12 bar and 80 °C. After finishing the hydrogen uptake (7 h), the catalyst was filtered off and the filtrate was evaporated *in vacuo* to give a dark green solid in quantitative yield (2.04 g, 6.32 mmol). Mp: 48 °C; $[\alpha]^{22}_D$ = −10.0 (*c* 1, CH_3OH); R_f = 0.26 ($CHCl_3$/MeOH = 9:1); ^1H NMR (300 MHz, $CDCl_3$) δ 6.42 (s, 1H, 4′/6′-H_{Ar}), 6.40 (s, 1H, 6′/4′-H_{Ar}), 5.94 (s, 2H, OCH_2O), 4.09 (s, 1H, OH), 4.06−3.92 (m, 5H, OCH_2CH_2O and 3-H), 3.89 (s, 3H, OCH_3), 2.80−2.78 (m, 2H, 4-H, 5-H), 2.20 (br s, 2H, NH_2), 2.13 (dt, *J* = 14.4 and 3.0 Hz, 1H, 2-H_α), 1.94 (dd, *J* = 14.4 and 3.0 Hz, 1H, 2-H_β), 1.88 (dt, *J* = 17.1 and 3.0 Hz, 1H, 6-H_α), 1.78 (t, *J* = 12.3 Hz, 1H, 6-H_β); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.1 (2-C), 41.7 (6-C), 43.3 (5-C), 56.9 (OCH_3), 57.6 (4-C), 64.3 (OCH_2CH_2O), 65.1 (OCH_2CH_2O), 69.5 (3-C), 101.6 (4-C_{Ar}), 101.7 (OCH_2O), 108.1 (6-C_{Ar}), 108.7 (1-C), 134.5 (7a-C_{Ar}), 136.0 (5-C_{Ar}), 143.9 (7-C_{Ar}), 149.5 (3a-C_{Ar}); IR (KBr) 3494, 2891, 1635, 1513, 1452, 1316, 1196, 1134, 1091, 921 cm^{-1}; anal. calcd for $C_{16}H_{21}NO_6$ (323.34): C, 59.43; H, 6.55; N, 4.33; found C, 59.45; H, 6.56; N, 4.30.

*(3R,4S,5S)-(−)-3-Hydroxy-4-methoxycarbonylamino-5-(7-methoxybenzo[1,3]dioxol-5-yl)cyclohexanone Ethylene Acetal [(−)-(**20**)].* To a solution of aminoketal (−)-**19** (1.94 g, 6.00 mmol) in THF (37 mL) were added half of the required methyl chloroformate (0.47 mL, 0.59 g, 6.18 mmol) and aqueous 3% NaOH solution (15 mL) followed by the second half of methyl chloroformate (0.47 mL, 0.59 g, 6.18 mmol). The biphasic mixture was stirred vigorously at room temperature for 2 h, poured into H_2O (82 mL), and extracted with $CHCl_3$ (3 × 72 mL). The combined organic layer was dried over Na_2SO_4, and the solvent was evaporated *in vacuo* to give a pale yellow solid. Yield: 99% (2.28 g, 5.98 mmol). HPLC conditions: TADDOL AS-H (*n*-hexane/isopropyl alcohol = 8:2, flow rate 2.0 mL min^{-1}, 256 nm, 20 °C), $t_{(+)}$ = 14 min and $t_{(-)}$ = 20 min. Mp: 185−188 °C; $[\alpha]^{22}_D$ = −4.3 (*c* 1, $CHCl_3$), ee 99%; R_f = 0.73 ($CHCl_3$/MeOH = 9:1); ^1H NMR (300 MHz, $CDCl_3$) δ 6.42 (s, 2H, 4′-H_{Ar} and 6′-H_{Ar}), 5.93 (s, 2H, OCH_2O), 4.99 (d, *J* = 9.3 Hz, 1H, NH), 4.13−4.10 (m, 1H, 3-H), 4.03−3.97 (m, 4H, OCH_2CH_2O), 3.89 (s, 3H, OCH_3), 3.83−3.80 (m, 1H, 4-H), 3.58 (d, *J* = 8.7 Hz, 1H, OH), 3.52 (s, 3H, $NHCOOCH_3$), 2.92 (td, *J* = 12.3 and 2.7 Hz 1H, 5-H), 2.09 (dt, *J* = 14.1 and 2.7 Hz, 1H, 2-H_α), 2.01 (dd, *J* = 14.1 and 2.1 Hz, 1H, 2-H_β), 1.93 (dt, *J* = 12.9 and 3.0 Hz, 1H, 6-H_α), 1,84 (t, *J* = 13.2 Hz, 1H, 6-H_β); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.9 (2-C), 41.9 (5-C), 43.0 (6-C), 52.2 ($NHCOOCH_3$), 56.4 (4-C), 56.8 (OCH_3), 64.4 (OCH_2CH_2O), 65.1 (OCH_2CH_2O), 69.9 (3-C), 101.5 (OCH_2O), 102.0 (4-C_{Ar}), 107.2 (6-C_{Ar}), 108.7 (1-C), 134.2 (7a-C_{Ar}), 136.2 (5-C_{Ar}), 143.9 (7-C_{Ar}), 149.1 (3a-C_{Ar}), 156.5 ($NHCOOCH_3$); IR (KBr) 3477, 3355, 2927, 1723, 1638, 1541, 1516, 1450, 1319, 1129, 1073, 914 cm^{-1}; anal. calcd for $C_{18}H_{23}NO_8$ (381.38) C, 56.69; H, 6.08; N, 3.67; found C, 56.68; H, 6.06; N, 3.69.

*(1R,6S)-(−)-[6-(7-Methoxybenzo[1,3]dioxol-5-yl)-4-oxocyclohex-2-enyl]carbamic Acid Methyl Ester [(−)-(**21**)].* Carbamate (−)-**20** (2.25 g, 5.90 mmol) and *p*-toluenesulfonic acid monohydrate (2.01 g, 0.01 mol) were dissolved in acetone (140 mL). The reaction mixture was heated to reflux and stirred for 1 h. It was cooled to room temperature, poured into saturated $NaHCO_3$ solution (275 mL), and extracted with $CHCl_3$ (3 × 150 mL). The combined organic layer was dried over Na_2SO_4, and the solvent was evaporated *in vacuo* to give a white solid. Yield: 99% (1.86 g, 5.83 mmol). HPLC conditions: TADDOL AD-H (*n*-hexane/isopropyl alcohol = 8:2, flow rate 0.8 mL min^{-1}, 256 nm, 10 °C), $t_{(-)}$ = 18 min and $t_{(+)}$ = 21 min. Mp: 153−157 °C; $[\alpha]^{22}_D$ = −142.6 (*c* 1, $CHCl_3$), ee 93%; R_f = 0.51 ($CHCl_3$/acetone = 3:1); ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (d, *J* = 9.9 Hz, 1H, 2-H), 6.43 (s, 1H, 4′/6′-H_{Ar}), 6.40 (s, 1H, 6′/4′-H_{Ar}), 6.08 (dd, *J* = 10.2 and 1.8 Hz, 1H, 3-H), 5.97 (s, 2H, OCH_2O), 4.82 (br s, 1H, NH), 4.65−4.59 (m, 1H, 1-H), 3.90 (s, 3H, OCH_3), 3.62 (s, 3H, $NHCOOCH_3$), 3.23−3.14 (m, 1H, 6-H), 2.68−2.65 (m, 2H, 5-H_α and 5-H_β); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.3 (5-C), 48.1 (6-C), 52.6 ($NHCOOCH_3$), 53.5 (1-C), 56.7 (OCH_3), 101.4 (4-C_{Ar}), 101.8 (OCH_2O), 107.4 (6-C_{Ar}), 129.5 (3-C), 134.5 (7a-C_{Ar}), 135.0 (5-C_{Ar}), 143.9 (7-C_{Ar}), 149.5 (3a-C_{Ar}), 151.8 (2-C), 156.4 ($NHCOOCH_3$), 197.5 (4-C); IR (KBr) 3323, 2916, 1696, 1637, 1539, 1449, 1384, 1323, 1263, 1188, 1134, 1100, 1058, 930, 863, 836, 777 cm^{-1}; anal. calcd for $C_{16}H_{17}NO_6$ (319.31) C, 60.18; H, 5.37; N, 4.39; found C, 60.19; H, 5.36; N, 4.37.

*(1R,4S,6S)-(−)-[4-Hydroxy-6-(7-methoxybenzo[1,3]dioxol-5-yl)-cyclohex-2-enyl]carbamic Acid Methyl Ester [(−)-(**22**)].* A mixture of enone (−)-**21** (0.93 g, 2.89 mmol), anhydrous MeOH (110 mL), and anhydrous $CaCl_2$ (0.65 g, 5.82 mmol) was stirred at room temperature for 30 min. It was cooled to 0 °C, and $NaBH_4$ (0.16 g, 4.26 mmol) was added. It was further stirred for 2 h at 0 °C, poured into H_2O (124 mL), and extracted with EtOAc (3 × 80 mL). The combined organic layer was dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. Recrystallization of the crude product from 1:3 MeOH/H_2O gave a white solid. Yield: 96% (0.89 g, 2.77 mmol). HPLC conditions: TADDOL AD-H (*n*-hexane/isopropyl alcohol = 8:2, flow rate 0.8 mL min^{-1}, 256 nm, 10 °C), $t_{(-)}$ = 15 min and $t_{(+)}$ = 33 min. Mp: 172−174 °C; $[\alpha]^{22}_D$ = −143.0 (*c* 1, acetone), ee 99%; R_f = 0.44 ($CHCl_3$/acetone = 3:1); ^1H NMR (300 MHz, $CDCl_3$) δ 6.42 (s, 1H, 4′-H_{Ar}), 6.38 (s, 1H, 6′-H_{Ar}), 5.94 (s, 2H, OCH_2O), 5.82 (dd, *J* = 10.2 and 1.2 Hz, 1H, 3-H), 5.74 (d, *J* = 9.9 Hz, 1H, 2-H), 4.59 (br s, 1H, NH), 4.47−4.43 (m, 1H, 4-H), 4.32 (t, *J* = 10.4 Hz, 1H, 1-H), 3.89 (s, 3H, OCH_3), 3.56 (s, 3H, $NHCOOCH_3$), 2.63 (t, *J* = 11.4 Hz, 1H, 6-H), 2.26 (dd, *J* = 12.2 and 5.4 Hz, 1H, 5-H_α), 1.81 (td, *J* = 12.7 and 9.8 Hz, 1H, 5-H_β); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.7 (5-C), 46.5 (6-C), 52.1 ($NHCOOCH_3$), 53.5 (1-C), 56.7 (OCH_3), 67.7 (4-C), 101.3 (4-C_{Ar}), 101.4 (OCH_2O), 106.9 (6-C_{Ar}), 131.0 (2-C), 132.6 (3-C), 134.1 (7a-C_{Ar}), 136.5 (5-C_{Ar}), 143.5 (7-C_{Ar}), 149.1 (3a-C_{Ar}), 156.5 ($NHCOOCH_3$); IR (KBr) 3327, 2926, 1688, 1633, 1537, 1513, 1452, 1323, 1245, 1194, 1138, 1099, 1051, 819 cm^{-1}; anal. calcd for $C_{16}H_{19}NO_6$ (321.33) C, 59.81; H, 5.96; N, 4.36; found C, 59.82; H, 5.97; N, 4.34.

*(1R,4R,5S)-(+)-Benzoic Acid 5-(7-Methoxybenzo[1,3]dioxol-5-yl)-4-methoxycarbonylaminocyclohex-2-enyl Ester [(+)-(**23**)].* Enol (−)-**22** (0.97 g, 3.02 mmol) and Ph_3P (0.95 g, 3.63 mmol) were dissolved in anhydrous THF (47 mL) and cooled to 0 °C. Diisopropyl azodicarboxylate (0.73 mL, 0.75 g, 3.71 mmol) in anhydrous THF (2.2 mL) was added dropwise at 0 °C and stirred for 10 min. Benzoic acid (0.44 g, 3.60 mmol) was added, and the mixture was stirred at 0 °C for 45 min, then allowed to warm to room temperature and further stirred for 4 h. The solvent was removed *in vacuo*, and the product was isolated by column chromatography, as a white solid, on silica ($CHCl_3$/acetone = 20:1). Yield: 63% (0.81 g, 1.90 mmol). HPLC conditions: TADDOL AD-H (*n*-hexane/isopropyl alcohol = 8:2, flow rate 0.8 mL min^{-1}, 256 nm, 10 °C), $t_{(-)}$ = 20 min and $t_{(+)}$ = 26 min. Mp: 147−151 °C; $[\alpha]^{22}_D$ = +121.2 (*c* 1, $CHCl_3$), ee 97%; R_f = 0.59 ($CHCl_3$/acetone = 20:1); ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.5 Hz, 2H, 2″-H_{Bz} and 6″-H_{Bz}), 7.58 (t, *J* = 7.2 Hz, 1H, 4″-H_{Bz}), 7.46 (t, *J* = 7.5 Hz, 2H, 3″-H_{Bz} and 5″-H_{Bz}), 6.44 (s, 1H, 4′-H_{Ar}), 6.42 (s, 1H, 6′-H_{Ar}), 6.05−6.02 (m, 2H, 2-H and 3-H), 5.95 (s, 2H, OCH_2O), 5.53−5.52 (m, 1H, 1-H), 4.65 (br s, 1H, NH), 4.37 (t, *J* = 9.4 Hz, 1H, 4-H), 3.90 (s, 3H, OCH_3), 3.59 (s, 3H, $NHCOOCH_3$), 2.91 (td, *J* = 10.6 and 4.0 Hz, 1H, 5-H), 2.19−2.16 (m, 2H, 6-H_α and 6-H_β); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.0 (6-C), 42.5 (5-C), 52.2 ($NHCOOCH_3$), 53.1 (4-C), 56.8 (OCH_3), 66.8 (1-C), 101.4 (OCH_2O), 101.6 (4-C_{Ar}), 107.2 (6-C_{Ar}), 125.7 (2-C), 128.4 (3-C_{Bz} and 5-C_{Bz}), 129.7 (2-C_{Bz} and 6-C_{Bz}), 130.4 (1-C_{Bz}), 133.1 (4-C_{Bz}), 134.2 (7a-C_{Ar}), 135.8 (3-C), 136.5 (5-C_{Ar}), 143.6 (7-C_{Ar}), 149.1 (3a-C_{Ar}), 156.5 ($NHCOOCH_3$), 165.9 (Ph−CO); IR (KBr) 3296, 2937, 1718, 1686, 1633, 1548, 1512, 1452, 1434, 1270, 1135, 1093, 959, 930, 713 cm^{-1}; anal. calcd for $C_{23}H_{23}NO_7$ (425.43) C, 64.93; H, 5.45; N, 3.29; found C, 64.91; H, 5.47; N, 3.28.

(1R,2R,3R,4S,5S)-(+)-Benzoic Acid 2,3-Dihydroxy-5-(7-methoxybenzo[1,3]dioxol-5-yl)-4-methoxycarbonyl-

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*aminocyclohexyl Ester [(+)-(**24**)].* Benzoate (+)-**23** (0.50 g, 1.18 mmol) was dissolved in a mixture of THF (7.2 mL) and H_2O (1.2 mL). Subsequently *N*-methylmorpholine *N*-oxide (0.30 g, 2.54 mmol) and 4% aqueous OsO_4 solution (0.52 mL, 0.02 g, 0.08 mmol) were added under an Ar atmosphere and stirred at room temperature, under Ar, for 24 h. The reaction mixture was poured into a saturated $Na_2S_2O_3$ solution (47 mL) and extracted with EtOAc (4 × 40 mL). The combined organic layer was dried over $MgSO_4$, and the solvent was removed *in vacuo* to give a white solid. Yield: 99% (0.54 g, 1.18 mmol). HPLC conditions: TADDOL AD-H (*n*-hexane/isopropyl alcohol = 8:2, flow rate 2.0 mL min^{-1}, 256 nm, 10 °C), $t_{(+)}$ = 17 min and $t_{(-)}$ = 23 min. Mp: 82−86 °C; $[\alpha]^{22}_D$ = +60.0 (*c* 1, $CHCl_3$), ee 95%; R_f = 0.39 ($CHCl_3$/acetone = 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.5 Hz, 2H, 2″-H_{Bz} and 6″-H_{Bz}), 7.60 (t, *J* = 7.5 Hz, 1H, 4″-H_{Bz}), 7.49 (t, *J* = 7.5 Hz, 2H, 3″-H_{Bz} and 5″-H_{Bz}), 6.44 (s, 1H, 4′-H_{Ar}), 6.38 (s, 1H, 6′-H_{Ar}), 5.93−5.92 (m, 2H, OCH_2O), 5.42−5.41 (m, 1H, 1-H), 4.75 (d, *J* = 7.1 Hz, 1H, NH), 4.22 (s, 1H, 2-H), 4.04 (ddd, *J* = 10.9 and 10.1 and 7.1 Hz, 1H, 4-H), 3.99−3.95 (m, 1H, 3-H), 3.88 (s, 3H, OCH_3), 3.59 (s, 3H, $NHCOOCH_3$), 2.85 (td, *J* = 13.0 and 3.5 Hz 1H, 5-H), 2.31 (ddd, *J* = 14.0 and 13.0 and 2.3 Hz, 1H, 6-H_β), 2.04 (dt, *J* = 14.4 and 3.2 Hz, 1H, 6-H_α); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.1 (6-C), 42.9 (5-C), 52.6 ($NHCOOCH_3$), 55.7 (4-C), 56.8 (OCH_3), 70.2 (2-C), 71.4 (1-C), 74.0 (3-C), 101.5 (OCH_2O), 101.6 (4-C_{Ar}), 107.3 (6-C_{Ar}), 128.6 (3-C_{Bz} and 5-C_{Bz}), 129.7 (2-C_{Bz} and 6-C_{Bz}), 130.0 (1-C_{Bz}), 133.4 (4-C_{Bz}), 134.3 (7a-C_{Ar}), 135.4 (5-C_{Ar}), 143.7 (7-C_{Ar}), 149.3 (3a-C_{Ar}), 158.8 ($NHCOOCH_3$), 165.2 (Ph−CO); IR (KBr) 3396, 2950, 1712, 1635, 1513, 1452, 1434, 1316, 1274, 1096, 1044, 930, 825, 714 cm^{-1}; anal. calcd for $C_{23}H_{25}NO_9$ (459.45) C, 60.13; H, 5.48; N, 3.05; found C, 60.14; H, 5.46; N, 3.03.

*(1R,2S,3R,4S,5S)-(−)-Benzoic Acid 2,3-Diacetoxy-5-(7-Methoxybenzo[1,3]dioxol-5-yl)-4-methoxycarbonyl-aminocyclohexyl Ester [(−)-(**25**)].* *cis*-Diol (+)-**24** (0.53 g, 1.16 mmol) was dissolved in acetyl chloride (4.30 mL, 4.79 g, 0.06 mol) and stirred at room temperature for 24 h. The reaction mixture was added dropwise to a saturated $NaHCO_3$ solution (378 mL) at 0 °C. The product was extracted with $CHCl_3$ (3 × 80 mL), and the combined organic layer was dried over $MgSO_4$. The solvent was removed *in vacuo* to give a white solid. Yield: 99% (0.62 g, 1.14 mmol). HPLC conditions: TADDOL AD-H (*n*-hexane/isopropyl alcohol = 8:2, flow rate 2.0 mL min^{-1}, 256 nm, 10 °C), $t_{(+)}$ = 8 min and $t_{(-)}$ = 14 min. Mp: 92−96 °C; $[\alpha]^{22}_D$ = −22.4 (*c* 1, $CHCl_3$), ee 95%; R_f = 0.78 ($CHCl_3$/acetone = 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.5 Hz, 2H, 2″-H_{Bz} and 6″-H_{Bz}), 7.63 (t, *J* = 7.5 Hz, 1H, 4″-H_{Bz}), 7.51 (t, *J* = 7.5 Hz, 2H, 3″-H_{Bz} and 5″-H_{Bz}), 6.44 (s, 1H, 4′-H_{Ar}), 6.39 (s, 1H, 6′-H_{Ar}), 5.94 (s, 2H, OCH_2O), 5.50 (t, *J* = 3.4 Hz, 1H, 1-H/2-H), 5.37 (dd, *J* = 10.5 and 3.0 Hz, 1H, 3-H), 5.30 (q, *J* = 3.2 Hz, 1H, 1-H/2-H), 4.45 (d, *J* = 9.3 Hz, 1H, NH), 4.20−4.15 (m, 1H, 4-H), 3.89 (s, 3H, OCH_3), 3.53 (s, 3H, $NHCOOCH_3$), 3.00 (td, *J* = 10.4 and 7.0 Hz, 1H, 5-H), 2.24 (s, 3H, $OCOCH_3$), 2.06−2.18 (m, 2H, 6-H_α and 6-H_β), 2.03 (s, 3H, $OCOCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (CH_3CO), 21.1 (CH_3CO), 33.9 (6-C), 43.6 (5-C), 52.2 ($NHCOOCH_3$), 53.4 (4-C), 56.8 (OCH_3), 69.3 (2-C), 69.5 (1-C), 71.4 (3-C), 101.5 (OCH_2O), 101.6 (4-C_{Ar}), 107.5 (6-C_{Ar}), 128.7 (3-C_{Bz} and 5-C_{Bz}), 129.4 (1-C_{Bz}), 129.9 (2-C_{Bz} and 6-C_{Bz}), 133.6 (4-C_{Bz}), 134.3 (7a-C_{Ar}), 134.9 (5-C_{Ar}), 143.5 (7-C_{Ar}), 149.1 (3a-C_{Ar}), 156.5 ($NHCOOCH_3$), 164.9 (Ph−CO), 169.5 (CH_3CO), 170,9 (CH_3CO); IR (KBr) 2958, 2850, 1726, 1701, 1515, 1453, 1367, 1248, 1137, 1097, 1047, 820, 716 cm^{-1}; anal. calcd for $C_{27}H_{29}NO_{11}$ (543.52) C, 59.66; H, 5.38; N, 2.58; found C, 59.65; H, 5.39; N, 2.56.

*(2R,3S,4R,4aS,11bS)-Benzoic Acid 3,4-Diacetoxy-6,7-dimethoxy-1,2,3,4,4a,11b-hexahydro[1,3]dioxolo[4,5-j]phenanthridin-2-yl Ester (**26**).* Carbamate (−)-**25** (0.50 g, 1.06 mmol) and 4-dimethylaminopyridine (0.33 g, 3.22 mmol) were dissolved in anhydrous CH_2Cl_2 (27.7 mL) and cooled to 0 °C. A solution of triflic anhydride (0.94 mL, 1.58 g, 5.60 mmol) in anhydrous CH_2Cl_2 (4.7 mL) was added dropwise in 15 min. The reaction mixture was stirred for 22 h while it was allowed to warm to room temperature. After quenching the reaction, the mixture was extracted with saturated $NaHCO_3$ solution (267 mL), aqueous 20% HOAc (267 mL), and again saturated $NaHCO_3$ (267 mL). The organic phase was dried over $MgSO_4$ and evaporated *in vacuo* to give the crude product containing two regioisomers. Yield: 99% (0.55 g, 1.05 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.8 Hz, 2H, 2′-H_{Bz} and 6′-H_{Bz}), 7.58 (t, *J* = 7.5 Hz, 1H, 4′-H_{Bz}), 7.46 (t, *J* = 7.4 Hz, 2H, 3′-H_{Bz} and 5′-H_{Bz}), 6.53 (s, 1H, 11-H), 6.00−5.97 (m, 2H, OCH_2O), 5.55 (s, 1H, 3-H), 5.50 (dd, *J* = 10.6 and 2.8 Hz, 1H, 4-H), 5.49−5.42 (m, 1H, 2-H), 3.93 (s, 3H, OCH_3), 3.83 (s, 3H, Ar−$CNOCH_3$), 3.39 (dd, *J* = 13.4 and 10.7 Hz, 1H, 4a-H), 2.75 (td, *J* = 13.1 and 3.8 Hz, 1H, 11b-H), 2.58 (dt, *J* = 14.3 and 3.6 Hz, 1H, 1-H_α), 1.98−1.94 (m, 1H, 1-H_β); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1 (CH_3CO), 21.2 (CH_3CO), 27.8 (1-C), 34.2 (11b-C), 52.7 (Ar−$CNOCH_3$), 57.0 (4a-C), 60.9 (OCH_3), 69.2 (3-C), 69.6 (2-C), 72.5 (4-C), 99.8 (11-C), 101.6 (9-C), 113.0 (6a-C), 128.6 (3-C_{Bz} and 5-C_{Bz}), 129.4 (1-C_{Bz}), 129.9 (2-C_{Bz} and 6-C_{Bz}), 133.5 (4-C_{Bz}), 137.5 (7a-C), 138.4 (11a-C), 142.2 (7-C), 151.1 (10a-C), 160.7 (6-C), 165.2 (Ph−CO), 169.4 (CH_3CO), 170.5 (CH_3CO); anal. calcd for $C_{27}H_{27}NO_{10}$ (525.51) C, 61.71; H, 5.18; N, 2.67; found C, 61.73; H, 5.19; N, 2.65.

*(2R,3S,4R,4aS,11bS)-Benzoic Acid 3,4-Diacetoxy-7-methoxy-6-oxo-1,2,3,4,4a,5,6,11b-octahydro[1,3]dioxolo[4,5-j]phenanthridin-2-yl Ester (**27**).* Methoxyphenantridine **26** (0.53 g, 1.00 mmol) was dissolved in THF (12 mL), a 2 M aqueous HCl solution (12 mL) was added, and the mixture was stirred at room temperature for 24 h. The reaction mixture was poured into a saturated $NaHCO_3$ solution (200 mL) and extracted with $CHCl_3$ (3 × 50 mL). The combined organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was dissolved in acetyl chloride (9.9 mL, 10.93 g, 139.23 mmol) and stirred at room temperature for 21 h, poured into a saturated $NaHCO_3$ solution (500 mL) at 0 °C, and extracted with $CHCl_3$ (4 × 60 mL). The combined organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to give a pale brown solid. Yield: 99% (0.51 g, 0.99 mmol). R_f = 0.58 ($CHCl_3$/acetone = 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.5 Hz, 2H, 2-H_{Bz} and 6-H_{Bz}), 7.62 (t, *J* = 7.5 Hz, 1H, 4-H_{Bz}), 7.49 (t, *J* = 7.5 Hz, 2H, 3-H_{Bz} and 5-H_{Bz}), 6.51 (s, 1H, 11-H_{Ar}), 6.09 (s, 1H, NH), 6.02−5.99 (m, 2H, OCH_2O), 5.59−5.57 (m, 1H, 2-H/3-H), 5.45−5.44 (m, 1H, 2-H/3-H), 5.32 (dd, *J* = 10.8 and 2.7 Hz, 1H, 4-H), 4.08 (s, 3H, Ar-OCH_3), 3.77 (t, *J* = 11.7 Hz, 1H, 4a-H), 3.23−3.13 (m, 1H, 11b-H), 2.61−2.55 (m, 1H, 1-H_α), 2.13 (s, 3H, $OCOCH_3$), 2.12 (s, 3H, $OCOCH_3$), 2.06−2.02 (m, 1H, 1-H_β); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (CH_3CO), 20.8 (CH_3CO), 27.1 (1-C), 36.2 (11b-C), 52.2 (4a-C), 60.9 (OCH_3), 67.5 (3-C), 69.1 (2-C), 71.8 (4-C), 99.1 (11-C), 101.7 (9-C), 108.2 (6a-C), 128.7 (3-C_{Bz} and 5-C_{Bz}), 129.1 (1-C_{Bz}), 129.8 (2-C_{Bz} and 6-C_{Bz}), 132.8 (7a-C), 133.7 (4-C_{Bz}), 137.3 (11a-C), 142.0 (7-C), 152.1 (10a-C), 163.8 (Ph−CO), 164.9 (6-C), 169.2 (CH_3CO), 170.4 (CH_3CO); anal. calcd for $C_{26}H_{25}NO_{10}$ (511.48) C, 61.06; H, 4.93; N, 2.74; found C, 61.08; H, 4.95; N, 2.73.

*(2R,3S,4R,4aS,11bS)-(−)-Benzoic Acid 3,4-Diacetoxy-7-hydroxy-6-oxo-1,2,3,4,4a,5,6,11b-octahydro[1,3]dioxolo[4,5-j]-phenanthridin-2-yl Ester [(−)-(**28**)].* Lactam **27** (0.51 mg, 0.99 mmol) was dissolved in anhydrous MeCN (45.4 mL), and subsequently KI (0.17 mg, 1.02 mmol) and a 0.5 M solution of TMS-Cl (0.14 g, 0.16 mL, 1.30 mmol) in anhydrous MeCN were added. The reaction mixture was heated to 60 °C and stirred for 1.5 h. After quenching the reaction with H_2O (64 mL) added dropwise at 0 °C and extraction with EtOAc (3 × 50 mL), the combined organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to give the crude product. The major isomer was isolated by column chromatography on silica (*n*-hexane/EtOAc = 1:1). Yield: 54% (0.27 g, 0.53 mmol). Mp: 256−266 °C; $[\alpha]^{22}_D$ = −82.6 (*c* 1, $CHCl_3$); R_f = 0.63 (*n*-hexane/EtOAc = 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.28 (s, 1H, OH), 8.05 (d, *J* = 7.5 Hz, 2H, 2-H_{Bz} and 6-H_{Bz}), 7.60 (t, *J* = 7.5 Hz, 1H, 4-H_{Bz}), 7.47 (t, *J* = 7.5 Hz, 2H, 3-H_{Bz} and 5-H_{Bz}), 6.35 (s, 1H, 11-H), 6.04 (s, 3H, NH, OCH_2O), 5.61 (t, *J* = 3.9 Hz, 1H, 3-H), 5.44 (q, *J* = 3.3 Hz, 1H, 2-H), 5.35 (dd, *J* = 10.8 and 2.7 Hz, 1H, 4-H), 3.87 (t, *J* = 12.8 Hz, 1H, 4a-H), 3.24 (td, *J* = 12.6 and 3.3 Hz, 1H, 11b-H), 2.62 (dt, *J* = 14.2 and 3.6 Hz, 1H, 1-H_α), 2.13 (s, 3H, $OCOCH_3$), 2.11 (s, 3H, $OCOCH_3$), 2.01−1.96 (m, 1H, 1-H_β); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (CH_3CO), 20.8 (CH_3CO), 26.9 (1-C), 34.8 (11b-C), 52.9 (4a-C), 67.5 (3-C), 69.1 (2-C), 71.8 (4-C), 96.8 (11-C), 102.4 (9-C), 107.0 (6a-C), 128.7 (3-C_{Bz} and 5-C_{Bz}), 129.1 (1-C_{Bz}), 129.8 (2-C_{Bz} and 6-C_{Bz}), 133.2 (7a-C), 133.8 (4-C_{Bz}), 135.8 (11a-C), 146.5 (7-C), 153.0

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(10a-C), 164.9 (Ph−CO), 169.2 ($COCH_3$), 170.2 ($COCH_3$), 170.3 (6-C); IR (KBr) 3345, 2926, 1754, 1727, 1673, 1465, 1370, 1340, 1269, 1235, 1060, 1029, 929, 803, 712 cm^{-1}; anal. calcd for $C_{25}H_{23}NO_{10}$ (497.45) C, 60.36; H, 4.66; N, 2.82; found C, 60.35; H, 4.67; N, 2.82.

*(2R,3S,4R,4aS,11bS)-(−)-2,3,4,7-Tetrahydroxy-1,3,4,4a,5,11b-hexahydro[4,5-j]phenanthridin-6-one [(−)-trans-Dihydronarciclasine (−)-**1**].* To a solution of phenanthridone (−)-**28** (0.26 g, 0.52 mmol) in anhydrous THF (38 mL) was added dropwise a 0.5 M methanolic solution of NaOMe (21 mL) at room temperature and stirred for 1 h, while gradual salt precipitation was observed. After quenching the reaction mixture with a saturated NH_4Cl solution (106 mL) at room temperature it was extracted with EtOAc (3 × 100 mL), and the combined organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to give a white solid. Yield: 99% (0.16 g, 0.51 mmol). HPLC conditions: TADDOL AS-H (*n*-hexane/isopropyl alcohol = 8:2, flow rate 2.0 mL min^{-1}, 256 nm, 20 °C), $t_{(-)}$ = 12 min, $t_{(+)}$ = 18 min. Mp: 272−273 °C; $[\alpha]^{22}_D$ = −8.0 (*c* 0.25, THF), de 100%, ee 92%; R_f = 0.46 (EtOAc/MeOH = 10:1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.97 (s, 1H, Ar−OH), 7.51 (s, 1H, NH), 6.47 (s, 1H, 11-H), 6.03−6.01 (m, 2H, OCH_2O), 5.13 (s, 1H, OH), 5.00 (s, 1H, OH), 4.95 (s, 1H, OH), 3.88 (s, 1H, 2-H), 3.75−3.70 (m, 2H, 3-H and 4-H), 3.32 (dd, *J* = 12.8 and 10.4 Hz, 1H, 4a-H), 2.85 (td, *J* = 12.5 and 3.2 Hz, 1H, 11b-H), 2.09 (dt, *J* = 13.4 and 3.4 Hz, 1H, 1-H$_\alpha$), 1.63 (td, *J* = 13.0 and 2.1 Hz, 1H, 1-H$_\beta$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.4 (1-C), 34.0 (11b-C), 55.4 (4a-C), 68.7 (4-C), 69.8 (2-C/3-C), 71.9 (2-C/3-C), 96.9 (11-C), 102.1 (9-C), 107.1 (6a-C), 132.2 (7a-C), 138.7 (11a-C), 145.6 (7-C), 152.5 (10a-C), 170.0 (6-C); IR (KBr) 3421, 2921, 2852, 1671, 1466, 1339, 1262, 1229, 1079, 1031, 918, 803, 582 cm^{-1}; anal. calcd for $C_{14}H_{15}NO_7$ (309.27) C, 54.37; H, 4.89; N, 4.53; found C, 54.35; H, 4.88; N, 4.52.

General Procedure for the Preparation of Chinchona-Based Organocatalysts. To a solution of cinchonine or quinine (18.5 mmol) in anhydrous THF (60 mL) was added Ph_3P (22 mmol), and the reaction mixture was cooled to 0 °C. Diisopropyl azodicarboxylate (22 mmol) was added dropwise, and the reaction mixture was stirred for 10 min. Next, diphenylphosphoryl azide (22 mmol) was added dropwise, and the reaction mixture was allowed to warm to room temperature. After stirring for 4 h at room temperature, it was heated to 45 °C and stirred for 3 h. Ph_3P (22 mmol) was added carefully (N_2 released) and stirred for a further 2 h. After that, the reaction was quenched with H_2O (6 mL) and stirred overnight. The solvent was evaporated *in vacuo*, and the residue was dissolved in CH_2Cl_2 (60 mL). It was extracted with a 2 M HCl solution (2 × 50 mL). The aqueous layer was purified with CH_2Cl_2 (2 × 35 mL). The aqueous phase was evaporated *in vacuo* to obtain a yellow solid. The crude product was recrystallized from a 1:1 EtOAc/MeOH mixture (50 mL) to give a pale yellow hydrochloride salt. It was dissolved in water (100 mL), a 25% NH_4OH solution (25 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 60 mL). The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to give an orange oil.

*(8R,9R)-9-Amino(9-deoxy)epicinchonine (**15**).* Yield: 85%; $[\alpha]^{22}_D$ = +104 (*c* 0.5, $CHCl_3$) {lit. $[\alpha]^{25}_D$ = +105 (*c* 1.0, $CHCl_3$)[22a]}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (d, *J* = 4.5 Hz, 1H, 2-H$_{quin}$), 8.35 (d, *J* = 5.4 Hz, 1H, 5-H$_{quin}$), 8.13 (dd, *J* = 8.4 and 0.6 Hz, 1H, 8-H$_{quin}$), 7.71 (td, *J* = 7.2 and 1.2 Hz, 1H, 7-H$_{quin}$), 7.59 (dd, *J* = 7.2 and 1.2 Hz, 1H, 3/6-H$_{quin}$), 7.56 (dd, *J* = 6.9 and 1.2 Hz, 1H, 3/6-H$_{quin}$), 5.85 (ddd, *J* = 16.8 and 10.8 and 6.9 Hz, 1H, CH_2=*CH*), 5.08 (d, *J* = 1.8 Hz, 1H, HC*H*=CH), 5.04 (dt, *J* = 7.8 and 1.2 Hz, 1H, *H*CH=CH), 4.75 (d, *J* = 9.6 Hz, 1H, H_2N-*CH*), 3.08−2.89 (m, 5H, 2-H$_{\alpha\ quinuc}$, 6-H$_{quinuc}$, 8-H$_{quinuc}$, 2-H$_{quinuc}$, and 6-H$_{quinuc}$), 2.26 (q, *J* = 8.1 Hz, 1H, 3-H$_{quinuc}$), 2.08 (s, 2H, NH_2), 1.58−1.50 (m, 3H, 4-H$_{quinuc}$, 5-H$_{\alpha\ quinuc}$, and 5-H$_{\beta\ quinuc}$), 1.10 (dd, *J* = 13.2 and 9.0 Hz, 1H, 7-H$_{quinuc}$), 0.97−0.90 (m, 1H, 7-H$_{quinuc}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0 (7-C$_{quinuc}$), 26.6 (5-C$_{quinuc}$), 27.6 (4-C$_{quinuc}$), 37.5 (H_2N−CH), 39.6 (3-C$_{quinuc}$), 47.4 (6-C$_{quinuc}$), 49.5 (2-C$_{quinuc}$), 62.2 (8-C$_{quinuc}$), 114.5 (CH_2-CH), 119.6 (3-C$_{quin}$), 123.3 (5-C$_{quin}$), 126.3 (6-C$_{quin}$), 127.8 (4a-C$_{quin}$), 128.9 (7/8-C$_{quin}$), 130.4 (7/8-C$_{quin}$), 140.5 (CH_2−*CH*), 148.5 (4-C$_{quin}$), 148.9 (8a-C$_{quin}$), 150.3 (2-C$_{quin}$).

*(8S,9S)-9-Amino(9-deoxy)epiquinine (**16**).* Yield: 87%; $[\alpha]^{22}_D$ = +103 (*c* 0.524, $CHCl_3$) {lit. $[\alpha]^{25}_D$ = +80 (*c* 1.1, $CHCl_3$)[22a]}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (d, *J* = 4.5 Hz, 1H, 2-H$_{quin}$), 8.04 (d, *J* = 9.3 Hz, 1H, 8-H$_{quin}$), 7.65 (br s, 1H, 5-H$_{quin}$), 7.47 (d, *J* = 4.2 Hz, 1H, 3-H$_{quin}$), 7.39 (dd, *J* = 9.3 and 2.7 Hz, 1H, 7-H$_{quin}$), 5.81 (ddd, *J* = 17.1 and 10.0 and 7.5 Hz, 1H, CH_2=*CH*), 5.02 (dt, *J* = 17.1 and 1.5 Hz, 1H, HC*H*=CH), 4.99 (d, *J* = 10.1 Hz, 1H, *H*CH=CH) 4.60 (d, *J* = 9.9 Hz, 1H, H_2N-*CH*), 3.98 (s, 3H, Ar-OCH_3), 3.29 (dd, *J* = 13.8 and 10.2 Hz, 1H, 2-H$_{\alpha\ quinuc}$), 3.21 (q, *J* = 6.9 Hz, 1H, 6-H$_{quinuc}$), 3.09 (q, *J* = 8.1 Hz, 1H, 8-H$_{quinuc}$), 2.86−2.76 (m, 2H, 2-H$_{quinuc}$ and 6-H$_{quinuc}$), 2.30−2.22 (m, 1H, 3-H$_{quinuc}$), 2.01 (s, 2H, NH_2), 1.64−1.54 (m, 3H, 4-H$_{quinuc}$, 5-H$_{\alpha\ quinuc}$ and 5-H$_{\beta\ quinuc}$), 1.44 (t, *J* = 10.8 Hz, 1H, 7-H$_{quinuc}$), 0.77 (dd, *J* = 12.8 and 6.8 Hz, 1H, 7-H$_{quinuc}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.0 (7-C$_{quinuc}$), 27.6 (4-C$_{quinuc}$), 28.1 (5-C$_{quinuc}$), 39.8 (3-C$_{quinuc}$), 41.0 (6-C$_{quinuc}$), 55.6 (OCH_3 and H_2N−CH_2), 56.3 (2-C$_{quinuc}$), 61.9 (8-C$_{quinuc}$), 102.0 (5-C$_{quin}$), 114.4 (CH_2−*CH*), 121.3 (3-C$_{quin}$ and 7-C$_{quin}$), 128.8 (4a-C$_{quin}$), 131.9 (8-C$_{quin}$), 141.7 (CH_2-CH), 144.8 (8a-C$_{quin}$), 146.9 (4-C$_{quin}$), 147.9 (2-C$_{quin}$), 157.7 (6-C$_{quin}$).

Preparation of Single Crystals of Compounds (*S*)-(−)-13 and (−)-17. For determining the absolute configurations of compounds (−)-**13** and (−)-**17**, single crystals were grown as follows. For (−)-**13**, a small portion of the pure product (0.2 g) was dissolved in methanol (10 mL), and it was allowed to crystallize at room temperature for 10 d, while for compound (−)-**17** (0.1 g) an isopropyl alcohol solution (10 mL) was made and it was also crystallized at room temperature for 10 d. Well-developed single crystals were formed that proved to be suitable for the single-crystal X-ray diffraction measurements. The crystallographic data were obtained in the Biostruct Laboratory at the Budapest University of Technology and Economics and are summarized in Tables S1 and S2 (Supporting Information).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.7b00208.

Copies of ^{1}H and ^{13}C NMR spectra for compounds (−)-**1**, **9**−(*S*)-(−)-**13**, **15**, **16**, and (−)-**16**−(−)-**27**, as well as chiral HPLC chromatograms of compounds (−)-**1**, (*S*)-(−)-**13**, (−)-**17**, (+)-**18**, and (−)-**20**−(−)-**25** (PDF)

Crystallographic data of compound (*S*)-(−)-**13** (CIF)

Crystallographic data of compound (−)-**17** (CIF)

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Notes

The authors declare no competing financial interest.

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