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Conversion of the Enzymatically Derived (1*S*,2*S*)-3-Bromocyclohexa-3,5-diene-1,2-diol into Enantiomerically Pure Compounds Embodying the Pentacyclic Framework of Vindoline

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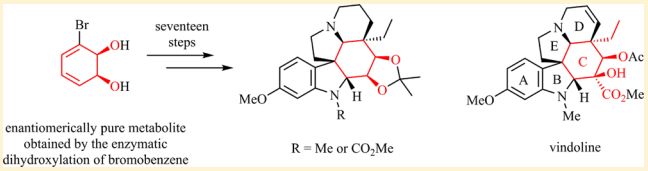
Supporting Information

ABSTRACT: The enzymatically derived and enantiomerically pure (1*S*,2*S*)-3-bromocyclohexa-3,5-diene-1,2-diol (**7**) has been elaborated over 17 steps into compounds **8** and **32**, each of which embodies the pentacyclic framework and much of the functionality associated with the alkaloid vindoline (**3**). This work sets the stage for effecting the conversion of the related metabolite (1*S*,6*R*)-5-ethyl-1,6-dihydroxycyclohexa-2,4-diene-1-carboxylic acid (**4**) into compound **3**, the latter being a biogenetic precursor to the clinically significant anticancer agents vinblastine and vincristine.



INTRODUCTION

The alkaloids vinblastine (**1**) and vincristine (**2**) (Figure 1) have been isolated from various sources, most notably the

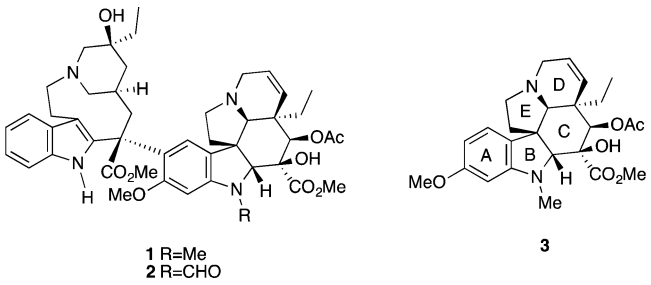


Figure 1. Structures of vinblastine, vincristine, and vindoline.

flowering plant *Vinca rosea* (*Catharanthus roseus* G. Don), a Madagascan rosy periwinkle, and each is used clinically in the treatment of a range of pathologies including Hodgkin's lymphoma and certain brain and bladder cancers.[1] They exert their beneficial therapeutic effects by binding to tubulin and thereby inhibiting mitosis.[2] Biogenetically speaking, compounds **1** and **2** are produced through the coupling of vindoline (**3**) and catharanthine,[3] and the effective *in vitro* mimicking of this process as well as the development of alternatives have been described and exploited in various contexts.[4]

The elaborate molecular architectures of vinblastine (**1**) and vincristine (**2**), their profoundly important medical value, issues of supply, the development of resistance to these drugs, and the need to establish structure−activity relationship (SAR) profiles have prompted considerable efforts to develop *de novo* syntheses of them. Necessarily, this has involved the establishment of routes to vindoline.[5,6] In 2002, Fukuyama and coworkers claimed the first efficient total synthesis of (−)-vindoline,[7] thus providing access to vinblastine (**1**) and vincristine (**2**) through the above-mentioned coupling process.[8] Spectacular additional contributions from the group of Boger[4a,9,10] have provided extraordinarily effective means for assembling the pentacyclic framework of the Eastern hemispheres of compounds **1** and **2** (as embodied in vindoline) and related systems. This type of work has also established an important understanding of the SAR profile within the class and allowed for the synthesis, through enhanced functionalization, of compounds that are significantly more potent than vinblastine and/or display reduced resistance by ameliorating Pgp-based drug efflux processes.[10,11] Such efforts stand as testimony to powerful methodological developments that can be made by targeting complex natural products such as **1** and **2** for synthesis.[10]

In 2005 we reported[12] a whole-cell biotransformation of *m*-ethyltoluene that allowed for its enantioselective conversion into the *cis*-1,2-dihydrocatechol **4** (Figure 2). Since this metabolite embodies key structural components associated with the highly functionalized C-ring of vindoline, we sought to establish means by which to effect the conversion **4** → **3**. As part of such a program, we recently reported[13] the outcomes of a model study wherein we were able to convert cyclohexane-1,4-dione monoethylene ketal (representing the developing C-ring of the eventual target **3**) into the tetracyclic but racemic amide **5**. This last compound could itself be engaged in a gold(I)-catalyzed cyclization reaction that afforded (after hydrolysis) the unsaturated lactam **6** (33%), thus establishing the pentacyclic framework of natural product **3**. While encouraging in various respects, the reaction sequence used did not seem readily amenable to modification so that a C-ring precursor such as metabolite **4** could be incorporated within it. Accordingly, we now detail the outcomes of a study that have

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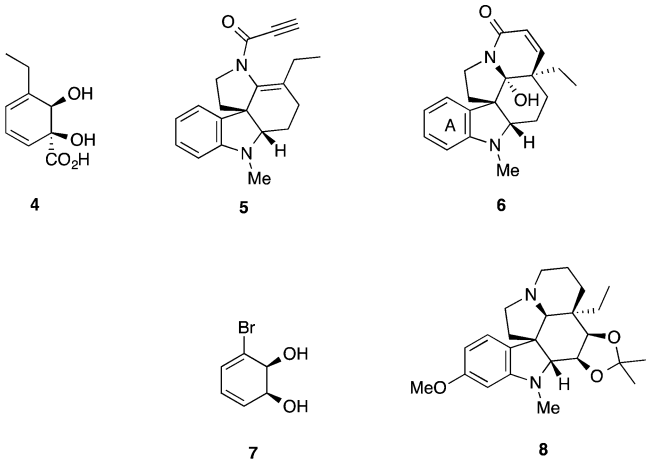


Figure 2. Metabolites **4** and **7**, previously prepared vindoline analogue **6**, its precursor **5**, and target compound **8**.

allowed for the conversion of the enantiomerically pure *cis*-1,2-dihydrocatechol **7**, a chiron that is available in kilogram if not tonne quantities through the whole-cell biotransformation of bromobenzene,[14] into a hexacyclic compound, **8**, that incorporates most of the structural elements of vindoline.

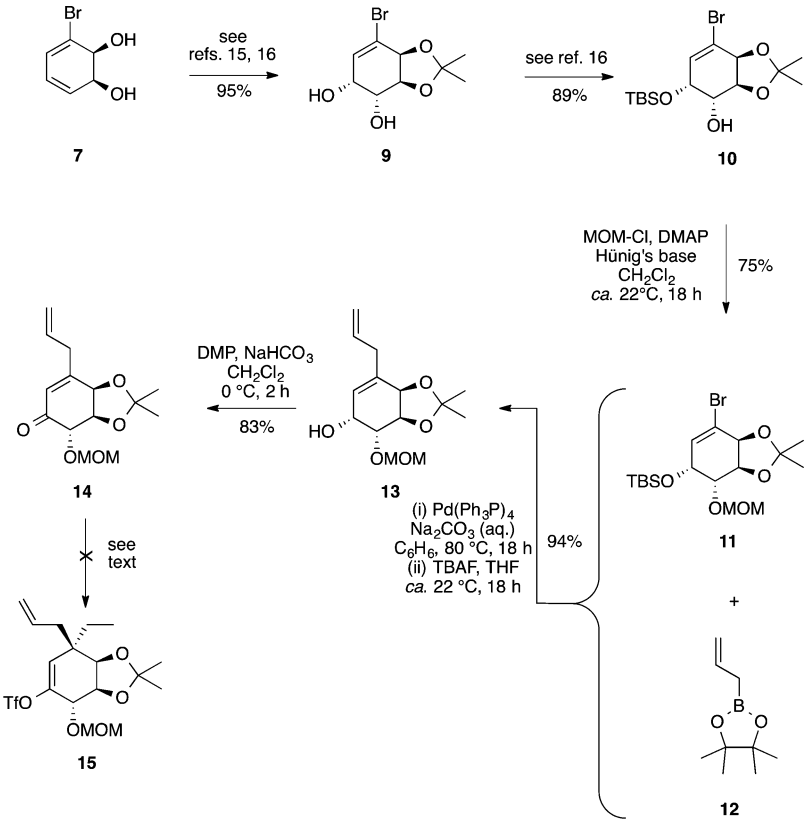
RESULTS AND DISCUSSION

Our initial efforts to deploy compound **7** as a starting material for the enantioselective preparation of the vindoline framework are shown in Scheme 1 and started with its regio- and stereoselective conversion, using established protocols, into the previously reported[15,16] bromoconduritol monoacetonide **9** (95% yield over two steps). Selective monoprotection of the allylic hydroxyl group within this last compound could be achieved by treating it with *tert*-butyldimethylsilyl chloride (TBS-Cl) in the presence of imidazole. The product, **10** (89%),[16] of this process was then reacted with chloromethyl-methyl ether (MOM-Cl) in the presence of 4-(*N*,*N*-dimethyl-amine)pyridine (DMAP) and *N*,*N*-di-isopropylethylamine (Hünig's base) to give the fully protected conduritol **11** (75%) that could itself be allylated in a Suzuki–Miyaura cross-coupling reaction with the commercially available boronate ester **12**. The product thus formed was immediately subjected to treatment with tetra-*n*-butylammonium fluoride (TBAF) and so delivering the allylic alcohol **13** in 94% yield over the two steps involved.

Oxidation of compound **13** with the Dess–Martin periodinane (DMP)[17] in the presence of sodium bicarbonate afforded the rather unstable 2-cyclohexen-1-one **14** (83%). Despite much effort, we were unable to carry this last compound forward in any useful fashion. For example, futile attempts were made to effect the conjugate addition of ethyl-containing nucleophiles to this potential Michael acceptor with trapping of the resulting enolate so as to generate compounds such as triflate **15**.[18]

Given the lack of success associated with efforts to establish the ethyl-bearing quaternary carbon center of vindoline through conjugate addition processes such as that shown in Scheme 1, other means for doing so were pursued. During the course of work concerned with the total synthesis of other alkaloids, we found that the Eschenmoser–Claisen rearrangement of various 3-substituted 2-cyclohexen-1-ols provided a uniquely effective means of establishing the necessary *β*,*β*,*β*-trisubstituted acetic acid derivative.[19] Accordingly we sought to apply this same

Scheme 1. Synthesis of 2-Cyclohexen-1-one 14



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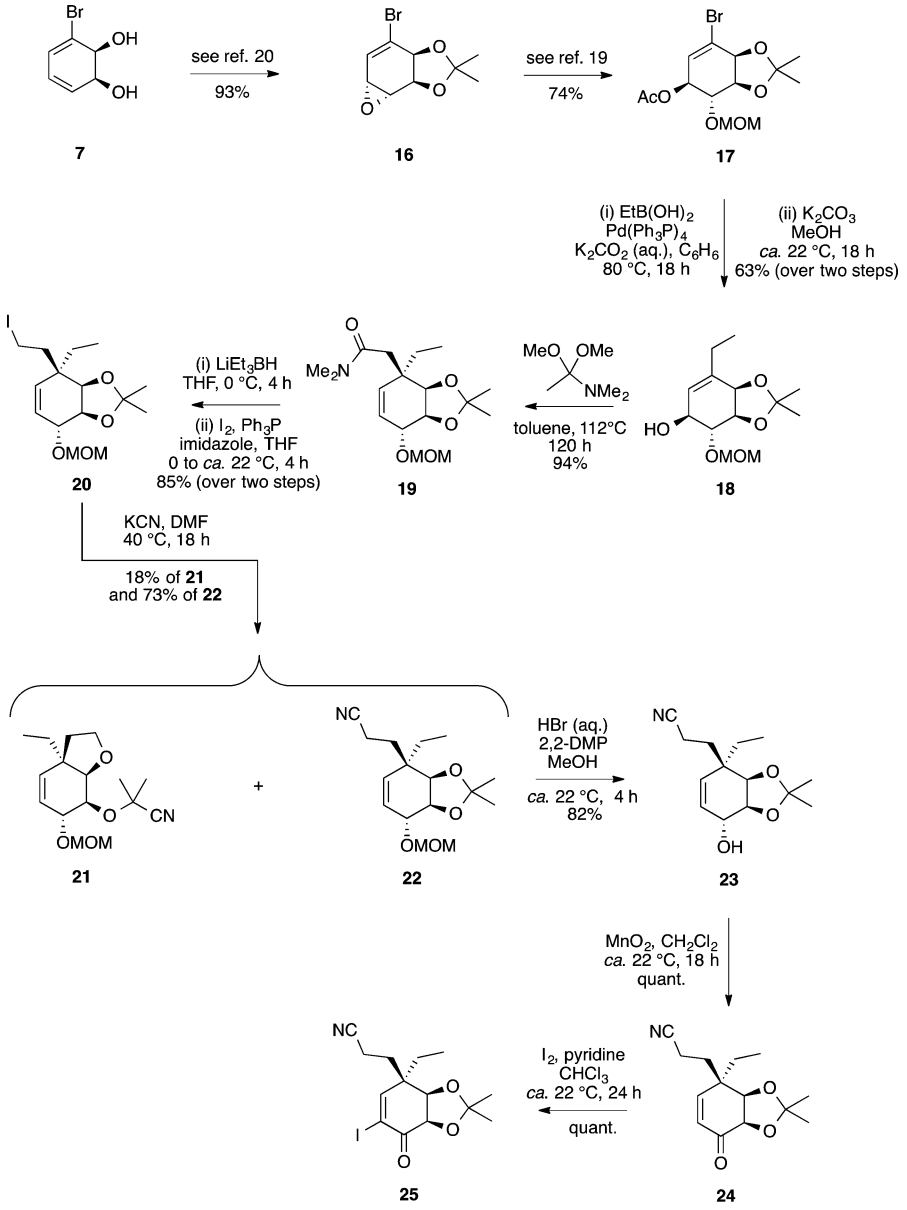
Scheme 2. Synthesis of Quaternary Carbon-Containing 2-Cyclohexen-1-one 25



protocol in the present setting, and the successful outcomes of our doing so are shown in Scheme 2. The opening stages of the reaction sequence were focused on the construction of the requisite 3-substituted 2-cyclohexen-1-ol and involved, as part of that process, the conversion of the *cis*-1,2-dihydrocatechol **7** into the previously reported epoxide **16**,[20] a process that can now be readily conducted on a rather large scale. Phosphoric acid catalyzed ring opening of the latter compound using acetic acid as the nucleophile proceeded in a completely regioselective manner and with inversion of configuration at the allylic carbon. The resulting alcohol was immediately protected as the corresponding MOM-ether **17**[19] (74% over two steps) under standard conditions. Cross-coupling of compound **17** with ethylboronic acid in the presence of tetrakis(triphenylphospine)palladium(0) and reaction of the resulting ethyl-substituted cyclohexene with methanolic potassium carbonate (so as to complete the partial cleavage of the acetate residue observed in the first step) afforded the allylic alcohol **18** (63%) sought as the substrate for the Eschenmoser−Claisen rearrangement.

When compound **18** was treated with *N*,*N*-dimethylacetamide dimethyl acetal in refluxing toluene the rearrangement reaction proceeded in the anticipated manner, so providing the *β*,*β*,*β*-trisubstituted acetic acid amide **19** in 94% yield. The assignment of the illustrated stereochemistry at the quaternary carbon within compound **19** is based on the well-recognized capacity of the Eschenmoser−Claisen rearrangement to faithfully transform an allylic alcohol of defined stereochemistry into a product that reflects this.[19] On reduction with lithium triethylborohydride, amide **19** afforded the corresponding alcohol that was immediately subjected to an Appel reaction[21] using molecular iodine in the presence of triphenylphosphine. This delivered the unstable iodide **20** in 85% yield. In the necessary final step of the side-chain homologation of rearrangement product **19**, compound **20** was treated with potassium cyanide. However, this reaction did not proceed entirely as expected. The close spatial relationship

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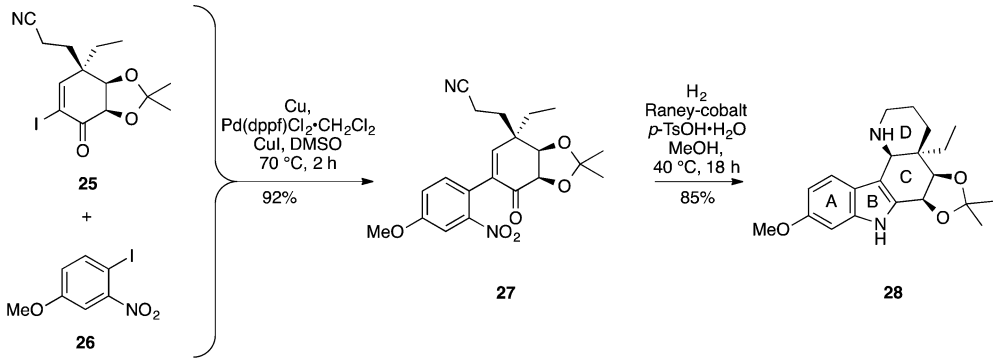
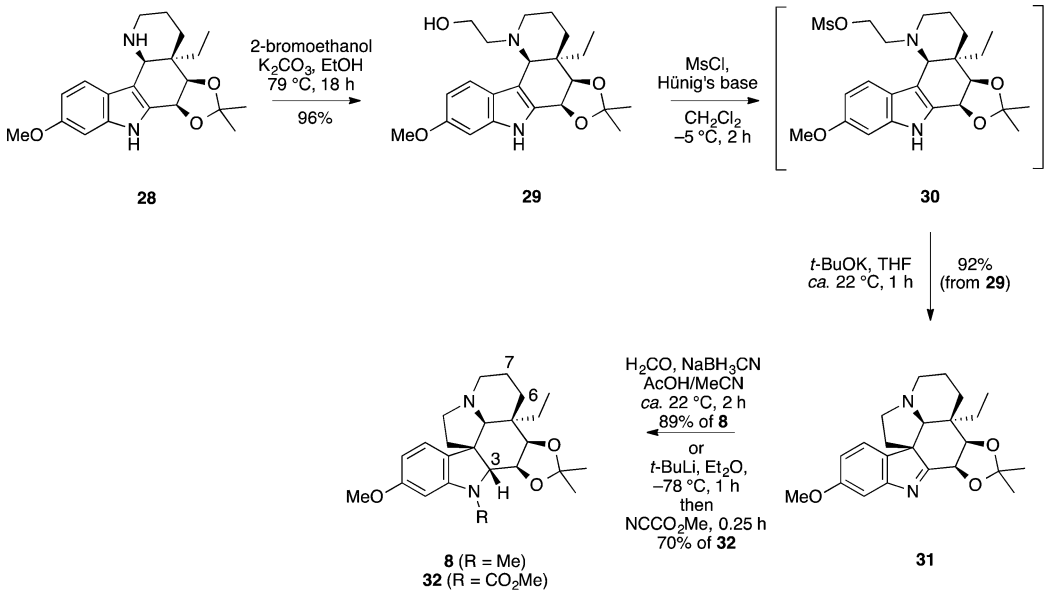
Scheme 3. Annulation of the A-, B-, and D-Rings to 2-Cyclohexen-1-one 25



Scheme 4. Establishing the E-Ring of Vindoline



between the iodine-bearing carbon and the nearer of the two acetonide oxygens in substrate **20** resulted in an intramolecular nucleophilic substitution reaction involving these two centers with the oxonium ion so-formed being attacked by the cyanide ion to afford the tetrahydrofuran **21** (18%) as well as the chromatographically separable, direct substitution product **22** (73%). Cleavage of the MOM-ether unit within compound **22** could be achieved using aqueous hydrogen bromide, but this was accompanied by partial hydrolysis of the acetonide residue. As a result it was more effective to treat a solution of substrate **22** in 2,2-DMP/methanol with HBr in order to smoothly generate (i.e. without accompanying cleavage of the acetonide unit) the allylic alcohol **23**.

Compound **23** was immediately oxidized, using manganese dioxide, to the corresponding enone **24** which was obtained in 82% overall yield from precursor **22**. Johnson-type α-iodination[22] of compound **24** was readily achieved using molecular iodine in the presence of pyridine, so generating the substrate, **25** (quant.), needed for the indole and piperidine annulation processes that would thereby establish the AB- and D-ring systems of the developing vindoline framework.

During the course of studies on the synthesis of the alkaloid limaspermidine[23] we identified a two-step protocol that enabled the simultaneous annulation of indole and piperidine ring systems to a γ,γ-disubstituted 2-aryl-2-cyclohexen-1-one and sought to apply this methodology in the present setting. Accordingly, compound **25** was engaged in a palladium-catalyzed Ullmann cross-coupling reaction[24] with the commercially available aryl iodide **26** (Scheme 3) and so delivering the α-arylated cyclohexenone **27** (92%). Compound **27** could be engaged in a reductive cyclization process using dihydrogen in the presence of Raney cobalt,[25] thereby producing the indole/piperidine **28** (85%) embodying the ABCD-tetracyclic ring system of vindoline.

In principle, there are various possible pathways available for the annulation of the required E-ring of vindoline to the tetracyclic framework of compound **28**, perhaps the most notable being that deployed by Heathcock[26] during the course of a synthesis of the alkaloid aspidospermadine. Given our successful exploitation of this protocol in various contexts,[23,27] we sought to apply it in the present case but without success. So, while the *N*-α-chloroacetamide derivative of compound **28** was readily prepared it could not be engaged in the required 5-*exo*-tet cyclization reaction.

The eventually successful E-ring annulation process is shown in Scheme 4 and began with the hydroxyethylation of the piperidine nitrogen of compound **28** using 2-bromoethanol as the electrophile[28] and potassium carbonate as the base. Mesylation of the product β-aminoalcohol **29** under the Crossland–Servis conditions[29] provided the anticipated and

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somewhat unstable sulfonate ester **30** that was immediately treated with potassium *tert*-butoxide.[30] As a result the desired pentacycle **31** (92% from **29**) was obtained. At this point, we sought to exploit the isoindole subunit embedded within this last compound for the purposes of inserting relevant additional substituents into the vindoline framework. Reductive methylation of imine **31** was readily achieved by treating it with formaldehyde in the presence of sodium cyanoborohydride and generating the *N*-methylindoline **8** in 80% yield. The assignment of the illustrated stereochemistry at C3 in this product has been made on the basis that only the *cis*-mode of fusion between rings B and C is feasible. In a somewhat more unusual transformation, successive treatment of substrate **31** with *tert*-butyllithium and then Mander's reagent[31] afforded the reductively *N*-carbomethoxylated compound **32** (70%) rather than the hoped for imine-containing and C3-carbomethoxylated product. In this conversion (*viz.* **31** → **32**), the *tert*-butyllithium is most likely serving as a hydride source[32] and with the resulting *N*-lithiated indoline then reacting with the added electrophile to deliver the observed product. All the spectral data derived from the final products **8** and **32** were in complete accord with the assigned structures.

CONCLUSIONS

The reaction sequences detailed herein enhance the prospects of being able to transform the homochiral metabolite (1*S*,6*R*)-5-ethyl-1,6-dihydroxycyclohexa-2,4-diene-1-carboxylic acid (**4**) into vindoline. Perhaps the greatest challenge in doing so is the devising of a protocol for introducing the carbon−carbon double bond present in the D-ring of the natural product. That said, Boger has identified potent vinblastine analogues that lack the $\Delta^{6,7}$-double bond within the vindoline subunit,[11d] and so it might be reasonable to conclude that this is not such a substantial issue in terms of generating active compounds. The outcome of studies focused on elaborating compound **4** into vindoline and various active analogues, including those embodying a five-membered D-ring,[11d] will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Procedures. Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for protons and 101 MHz for carbon nuclei. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. Infrared spectra (ν_{max}) were recorded on an FTIR spectrometer. Samples were analyzed as thin films on KBr plates. Optical rotations were recorded in the indicated solvent at 20 °C. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph−mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (conc.)/water (37.5 g/7.5 g/37.5 g/720 mL) or potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g/20 g/5 mL/300 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[33] with silica gel 60 (40−63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents, drying agents, and other inorganic salts were generally commercially available and used as supplied. Tetrahydrofuran (THF), methanol, and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.[34] Petroleum spirit refers to that hydrocarbon fraction boiling in the range between 40 and 60 °C. Where necessary, reactions were performed under an atmosphere of nitrogen.

*(((3a*S*,4*S*,5*R*,7a*S*)-7-Bromo-4-(methoxymethoxy)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxol-5-yl)oxy)(tert-butyl)-dimethylsilane (**11**).* A magnetically stirred solution of compound **10**[16] (9.84 g, 25.9 mmol) in dichloromethane (50 mL) maintained under an atmosphere of nitrogen at room temperature was treated, successively, with Hünig's base (27.1 mL, 155.7 mmol, 6 mol equiv), DMAP (3.17 g, 25.9 mmol, 1 mol equiv), and freshly prepared MOM-Cl (9.85 mL, 130.0 mmol, 5 molar equiv). After 18 h the reaction mixture was quenched via the slow addition of $NaHCO_3$ (150 mL of a saturated aqueous solution), and the separated aqueous phase was extracted with dichloromethane (1 × 100 mL). The combined organic phases were washed with NH_4Cl (1 × 150 mL of a saturated aqueous solution), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:20 v/v ethyl acetate/petroleum spirit elution), and concentration of the relevant fractions (R_f = 0.4 in 1:10 v/v ethyl acetate/petroleum spirit) afforded bromide **11** (8.24 g, 75%) as a clear, colorless oil, $[\alpha]_D$ = −80.2 (c = 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (d, J = 2.8 Hz, 1H), 4.82 (d, J = 6.7 Hz, 1H), 4.72 (d, J = 6.7 Hz, 1H), 4.64 (d, J = 5.4 Hz, 1H), 4.44 (dd, J = 5.4 and 1.1 Hz, 2H), 4.07 (app. t, J = 4.3 Hz, 1H), 3.39 (s, 3H), 1.43 (s, 3H), 1.40 (s, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.7, 122.4, 110.1, 97.1, 76.8, 75.8, 75.5, 68.0, 55.7, 27.6, 26.2, 25.8, 18.1, − 4.8 (two signals overlapping); IR (KBr) ν_{max} 2931, 2892, 2857, 1643, 1472, 1371, 1254, 1117, 1079, 1040, 968, 874, 836, 777 cm^{-1}; MS (ESI, + ve) m/z 447 and 445 [(M + Na)$^+$, 100 and 93% respectively]; HRMS (ESI, + ve) [M + Na]$^+$ calcd for $C_{17}H_{31}{}^{79}BrNaO_5Si$ 445.1022, found 445.1022.

*(3a*R*,4*R*,5*R*,7a*R*)-7-Allyl-4-(methoxymethoxy)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxol-5-ol (**13**).* A vigorously stirred solution of bromide **11** (600 mg, 1.42 mmol) in degassed benzene (20 mL) maintained under an atmosphere of nitrogen at room temperature was treated with Na_2CO_3 (5 mL of a 2 M aqueous solution that had been degassed by sonicating it for 0.25 h under an atmosphere of nitrogen at room temperature). The ensuing two-phase system was treated with $Pd(PPh_3)_4$ (162 mg, 0.14 mmol, 0.1 mol equiv) and boronate ester **12** (400 μL, 2.13 mmol, 1.5 mol equiv) and then heated under reflux for 18 h. The cooled reaction mixture was diluted with water (10 mL), and the separated aqueous phase was extracted with diethyl ether (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The brown residue thus obtained was dissolved in THF (25 mL), and the solution so formed was treated, at room temperature, with TBAF (4.26 mL of a 1 M solution in THF, 4.26 mmol, 3 mol equiv). The resulting mixture was stirred for 18 h and then diluted with diethyl ether (10 mL) and $NaHCO_3$ (20 mL of a saturated aqueous solution). The separated aqueous phase was extracted with diethyl ether (2 × 50 mL), and the combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The black residue thus obtained was subjected to flash chromatography (silica, 1:3 v/v ethyl acetate/petroleum spirit elution), and concentration of the relevant fractions (R_f = 0.35 in 1:1 v/v ethyl acetate/petroleum spirit) afforded alcohol **13** (336 mg, 94%) as a clear, colorless oil, $[\alpha]_D$ = −95.5 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (m, 1H), 5.62 (d, J = 4.4 Hz, 1H), 5.14 (m, 1H), 5.08 (d, J = 1.3 Hz, 1H), 4.78 (ABq, J = 6.7 Hz, 2H), 4.51 (d, J = 5.9 Hz, 1H), 4.42 (app. t, J = 6.3 Hz, 1H), 4.30 (broad s, 1H), 3.88 (dd, J = 6.7 and 3.5 Hz, 1H), 3.40 (s, 3H), 3.02−2.81 (complex m, 2H), 2.74 (d, J = 6.0 Hz, 1H), 1.41 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 134.7, 124.9, 117.3, 109.3, 96.9, 77.9, 74.6, 74.2, 65.4,

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55.7, 37.7, 27.7, 26.1; IR (KBr) ν_{max} 3445, 2985, 2993, 2869, 1638, 1433, 1380, 1370, 1236, 1217, 1153, 1107, 1054, 1029, 917, 875 cm^{-1}; MS (ESI, + ve) m/z 293 [$(M + Na)^+$, 100%]; HRMS (ESI, + ve) [$M + Na]^+$ calcd for $C_{14}H_{22}NaO_5$ 293.1365, found 293.1365.

*(3aR,4S,7aR)-7-Allyl-4-(methoxymethoxy)-2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3]dioxol-5(4H)-one (**14**).* A magnetically stirred solution of alcohol **13** (118 mg, 0.47 mmol) in dichloromethane (12 mL) was cooled to 0 °C and then treated with $NaHCO_3$ (600 mg, 7.04 mmol, 15 mol equiv) and DMP (600 mg, 1.41 mmol, 3 mol equiv). After 2 h the reaction mixture was treated with $Na_2S_2O_3$ (10 mL of a saturated aqueous solution) and stirred for a further 0.5 h at 0 °C. The separated aqueous phase was extracted with dichloromethane (3 × 10 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and then concentrated under reduced pressure at 25 °C. The residue thus obtained was subjected to flash chromatography (silica, 1:3 v/v ethyl acetate/petroleum spirit elution), and concentration of the relevant fractions (R_f = 0.75 in 1:1 v/v ethyl acetate/petroleum spirit) afforded enone **14** (105 mg, 83%) as a clear, pale-yellow oil, $[\alpha]_D$ = −315.0 (c = 0.4, C_6H_6). ^{1}H NMR (400 MHz, C_6H_6) δ 5.81 (s, 1H), 5.52 (m, 1H), 4.98−4.89 (complex m, 2H), 4.92 (d, J = 6.6 Hz, 1H), 4.67 (d, J = 6.6 Hz, 1H), 4.45 (d, J = 6.4 Hz, 1H), 4.30−4.20 (complex m, 2H), 3.26 (s, 3H), 2.81 (dd, J = 16.8 and 6.5 Hz, 1H), 2.68 (dd, J = 16.8 and 7.4 Hz, 1H), 1.34 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 194.4, 154.7, 133.0, 126.0, 118.7, 110.7, 96.3, 77.5, 76.6, 73.8, 55.5, 38.4, 27.9, 26.5; IR (KBr) ν_{max} 2987, 2935, 2894, 1698, 1635, 1455, 1382, 1372, 1219, 1153, 1072, 1035, 919, 858 cm^{-1}; MS (ESI, + ve) m/z 291 [$(M + Na)^+$, 100%]; HRMS (ESI, + ve) [$M + H]^+$ calcd for $C_{14}H_{21}O_5$ 269.1389, found 269.1395.

*(3aR,4R,5S,7aR)-7-Ethyl-4-(methoxymethoxy)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxol-5-ol (**18**).* A vigorously stirred solution of bromide **17**[19] (1.00 g, 2.85 mmol) in degassed benzene (40 mL) maintained at room temperature under an atmosphere of nitrogen was treated with K_2CO_3 (10 mL of a degassed 2 M aqueous solution). The ensuing two-phase system was treated with $Pd(PPh_3)_4$ (659 mg, 0.57 mmol, 0.2 equiv) and ethyl boronic acid (632 mg, 8.55 mmol, 3 equiv) and then heated under reflux for 18 h. The cooled reaction mixture was diluted with water (20 mL), and the separated aqueous phase was extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the brown residue thus obtained was dissolved in methanol (50 mL). The resulting solution was treated with K_2CO_3 (ca. 100 mg) and the mixture so formed was stirred at room temperature for 18 h, then diluted with ethyl acetate (150 mL), and washed with brine (1 × 100 mL). The separated aqueous phase was extracted with ethyl acetate (3 × 50 mL), and the combined organic extracts were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The brown residue thus obtained was subjected to flash chromatography (silica, 1:3 → 1:1 v/v ethyl acetate/petroleum spirit gradient elution), and concentration of the relevant fractions (R_f = 0.5 in 1:1 v/v ethyl acetate/petroleum spirit) afforded alcohol **18** (468 mg, 63%) as a pale-yellow oil, $[\alpha]_D$ = +23.3 (c = 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (m, 1H), 4.83 (ABq, J = 6.8 Hz, 2H), 4.50 (d, J = 6.3 Hz, 1H), 4.15 (dd, J = 8.5 and 6.3 Hz, 1H), 4.05 (m, 1H), 3.89 (d, J = 3.2 Hz, 1H), 3.45 (s, 3H), 2.35−2.18 (complex m, 1H), 2.16−2.06 (complex m, 1H), 1.47 (s, 3H), 1.38 (s, 3H), 1.08 (t, J = 7.4 Hz, 3H) (signal due to OH group proton not observed); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.9, 125.2, 109.9, 97.9, 84.2, 76.4, 74.9, 69.3, 55.8, 28.1, 26.1, 25.8, 11.5; IR (KBr) ν_{max} 3438, 2984, 2935, 1457, 1371, 1244, 1218, 1153, 1109, 1072, 1042, 868 cm^{-1}; MS (EI, 70 eV) m/z 258 ($M^{+\bullet}$, 2%), 243 [$(M - \bullet CH_3)^+$, 13], 196 (8), 155 (10), 145 (100); HRMS (EI) $(M - \bullet CH_3)^+$ calcd for $C_{12}H_{19}O_5$ 243.1232, found 243.1232.

*2-((3aR,4R,7R,7aS)-4-Ethyl-7-(methoxymethoxy)-2,2-dimethyl-3a,4,7,7a-tetrahydrobenzo[d][1,3]dioxol-4-yl)-N,N-dimethylacetamide (**19**).* A stirred solution of alcohol **18** (3.33 g, 12.9 mmol) in toluene (190 mL) maintained under a nitrogen atmosphere at room temperature was treated with *N*,*N*-dimethylacetamide dimethyl acetal[35] (19 mL, 128.91 mmol, 10 equiv). The ensuing solution was heated under reflux for 120 h, and then the cooled reaction mixture was concentrated under reduced pressure. The dark brown oil thus obtained was subjected to flash chromatography (silica, 1:1 → 2:1 v/v ethyl acetate/petroleum spirit gradient elution), and concentration of the relevant fractions (R_f = 0.5 in 2:1 v/v ethyl acetate/petroleum spirit) afforded amide **19** (3.97 g, 94%) as a pale-yellow oil, $[\alpha]_D$ = −36.0 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (dd, J = 10.3 and 1.9 Hz, 1H), 5.70 (dd, J = 10.3 and 2.0 Hz, 1H), 4.86 (d, J = 6.7 Hz, 1H), 4.73 (d, J = 6.7 Hz, 1H), 4.27−4.16 (complex m, 3H), 3.40 (s, 3H), 2.99 (s, 3H), 2.90 (s, 3H), 2.57 (d, J = 16.0 Hz, 1H), 2.34 (d, J = 16.0 Hz, 1H), 1.96−1.71 (complex m, 2H), 1.44 (s, 3H), 1.34 (s, 3H), 0.87 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 135.9, 125.7, 107.9, 95.4, 79.5, 78.1, 74.4, 55.4, 41.2, 37.7, 36.4, 35.4, 30.3, 27.1, 25.0, 8.7; IR (KBr) ν_{max} 2935, 1651, 1394, 1380, 1212, 1150, 1099, 1042, 917 cm^{-1}; MS (EI, 70 eV) m/z 327 ($M^{+\bullet}$, 12%), 312 (18), 282 (23), 266 (100), 208 (45); HRMS (ESI, + ve) [$M + Na]^+$ calcd for $C_{17}H_{29}NNaO_5$ 350.1943, found 350.1944.

*2-((3aR,4R,7R,7aS)-4-Ethyl-7-(methoxymethoxy)-2,2-dimethyl-3a,4,7,7a-tetrahydrobenzo[d][1,3]dioxol-4-yl)ethan-1-ol (Product of Reduction of Compound **19**).* A magnetically stirred solution of amide **19** (6.00 g, 20.04 mmol) in THF (150 mL) maintained at 0 °C under an atmosphere of nitrogen was treated, in one portion, with Et_3BHLi (60 mL of a 1 M solution in THF, 60.13 mmol, 3 equiv). After 4 h methanol was added, dropwise via Pasteur pipette, to the reaction mixture until gas evolution had ceased [***CAUTION***]. The ensuing solution was concentrated under reduced pressure, and the residue thus obtained subjected to flash chromatography (silica, 1:3 → 1:1 v/v ethyl acetate/petroleum spirit gradient elution). Concentration of the relevant fractions (R_f = 0.4 in 1:1 v/v ethyl acetate/petroleum spirit) afforded the title product (5.74 g, quantitative) as a clear, colorless oil, $[\alpha]_D$ = −40.0 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (dd, J = 10.2 and 3.0 Hz, 1H), 5.48 (dd, J = 10.2 and 1.8 Hz, 1H), 4.83 (d, J = 6.7 Hz, 1H), 4.73 (d, J = 6.7 Hz, 1H), 4.19 (m, 2H), 4.07 (m, 1H), 3.69 (td, J = 6.4 and 1.4 Hz, 2H), 3.40 (s, 3H), 2.41 (broad s, 1H), 1.87 (m, 1H), 1.72 (m, 1H), 1.64−1.39 (complex m, 2H), 1.47 (s, 3H), 1.36 (s, 3H), 0.86 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.3, 126.3, 108.0, 95.6, 79.2(3), 79.1(7), 74.1, 59.1, 55.4, 40.9, 37.9, 32.2, 27.3, 25.5, 8.5; IR (KBr) ν_{max} 3436, 2935, 2886, 1462, 1380, 1242, 1213, 1151, 1099, 1044, 918, 877 cm^{-1}; MS (ESI, + ve) m/z 309 [$(M + Na)^+$, 100%]; HRMS (ESI, + ve) [$M + Na]^+$ calcd for $C_{15}H_{26}NaO_5$ 309.1678, found 309.1678.

*(3aR,4R,7R,7aS)-4-Ethyl-4-(2-iodoethyl)-7-(methoxymethoxy)-2,2-dimethyl-3a,4,7,7a-tetrahydrobenzo[d][1,3]dioxole (**20**).* A magnetically stirred solution of the above-mentioned product alcohol (480 mg, 1.67 mmol), PPh_3 (658 mg, 2.51 mmol, 1.5 equiv), and imidazole (228 mg, 3.35 mmol, 2 equiv) in THF (20 mL) maintained under an atmosphere of nitrogen at 0 °C was treated, in one portion, with a solution of molecular iodine (637 mg, 2.51 mmol, 1.5 equiv) in THF (5 mL). The ensuing mixture was allowed to warm to room temperature over 4 h, then diluted with diethyl ether (20 mL), and quenched with $NaHCO_3/Na_2S_2O_3$ (50 mL of a 1:1 v/v mixture of saturated aqueous solutions). The separated aqueous phase was extracted with diethyl ether (3 × 40 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The yellow residue thus obtained was subjected to flash chromatography (silica, 1:20 → 1:10 v/v ethyl acetate/petroleum spirit gradient elution), and concentration of the relevant fractions (R_f = 0.3 in 1:10 v/v ethyl acetate/petroleum spirit) afforded iodide **20** (563 mg, 85%) as a clear, yellow oil, $[\alpha]_D$ = −110.0 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (dd, J = 10.3 and 2.4 Hz, 1H), 5.45 (dd, J = 10.3 and 1.9 Hz, 1H), 4.86 (d, J = 6.7 Hz, 1H), 4.74 (d, J = 6.7 Hz, 1H), 4.21−4.12 (complex m, 2H), 4.00 (d, J = 6.1 Hz, 1H), 3.41 (s, 3H), 3.26−3.12 (complex m, 2H), 2.22−2.05 (complex m, 2H), 1.58−1.40 (complex m, 2H), 1.47 (s, 3H), 1.35 (s, 3H), 0.87 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.8, 127.7, 108.1, 95.6, 79.3, 78.4, 74.3, 55.5, 44.1, 40.6, 31.6, 27.2, 25.1, 8.5, 1.3; IR (KBr) ν_{max} 2929, 1461, 1380, 1213, 1151, 1100, 1042, 918, 873 cm^{-1}; MS (EI, 70 eV) m/z 396 ($M^{+\bullet}$, 3%), 381 (16), 309 (100), 296 (93), 277 (43), 267 (94); HRMS (EI) $M^{+\bullet}$ calcd for $C_{15}H_{25}IO_4$ 396.0798, found 396.0795.

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*2-(((3aR,6R,7S,7aR)-3a-Ethyl-6-(methoxymethoxy)-2,3,3a,6,7,7a-hexahydrobenzofuran-7-yl)oxy)-2-methylpropanenitrile (**21**) and 3-((3aR,4R,7R,7aS)-4-Ethyl-7-(methoxymethoxy)-2,2-dimethyl-3a,4,7,7a-tetrahydrobenzo[d][1,3]dioxol-4-yl)propanenitrile (**22**).* A solution of iodide **20** (495 mg, 1.25 mmol) in DMF (20 mL) maintained under an atmosphere of nitrogen at room temperature was treated, in one portion, with KCN (814 mg, 12.50 mmol, 10 equiv). The resulting suspension was stirred at 40 °C for 18 h, then cooled, diluted with water (20 mL), and extracted with diethyl ether (3 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 1:5 → 1:3 v/v ethyl acetate/petroleum spirit gradient elution) to afford two fractions, A and B.

Concentration of fraction A [R_f = 0.2(4) in 1:5 v/v ethyl acetate/petroleum spirit] afforded furan **21** (66 mg, 18%) as a clear, colorless oil, $[\alpha]_D$ = −80.6 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (dd, *J* = 10.3 and 1.8 Hz, 1H), 5.39 (dd, *J* = 10.3 and 1.8 Hz, 1H), 4.75 (ABq, *J* = 6.7 Hz, 2H), 4.31 (d, *J* = 8.5 Hz, 1H), 4.07 (s, 1H), 3.92−3.82 (complex m, 2H), 3.67 (m, 1H), 3.40 (s, 3H), 1.90−1.75 (complex m, 2H), 1.65 (s, 3H), 1.64, (m, 2H), 1.61 (s, 3H), 0.99 (td, *J* = 7.6 and 1.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.7, 128.1, 121.4, 97.2, 82.7, 78.2, 73.1, 70.7, 66.9, 55.5, 50.0, 38.3, 30.6, 28.6, 27.2, 10.0; IR (KBr) ν_{max} 2965, 2938, 2881, 1463, 1386, 1173, 1152, 1104, 1061, 917, 842, 774 cm^{-1}; MS (ESI, + ve) *m*/*z* 318 [(M + Na)$^+$, 100%]; HRMS (ESI, + ve) [M + Na]$^+$ calcd for $C_{16}H_{25}NNaO_4$ 318.1681, found 318.1681.

Concentration of fraction B [R_f = 0.2(6) in 1:5 v/v ethyl acetate/petroleum spirit] afforded compound **22** (281 mg, 73%) as a clear, colorless oil, $[\alpha]_D$ = −67.2 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (d, *J* = 10.2, 1H), 5.42 (d, *J* = 10.2, 1H), 4.79 (ABq, *J* = 6.7 Hz, 2H), 4.20−4.12 (complex m, 2H), 4.01 (m, 1H), 3.41 (s, 3H), 2.51−2.28 (complex m, 2H), 1.87 (m, 2H), 1.61−1.40 (complex m, 2H), 1.47 (s, 3H), 1.35 (s, 3H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.3, 128.4, 120.4, 108.2, 95.6, 79.1, 78.4, 73.9, 55.4, 41.2, 31.9, 31.1, 27.2, 25.2, 12.9, 8.4; IR (KBr) ν_{max} 2931, 2246, 1737, 1654, 1462, 1381, 1261, 1242, 1213, 1151, 1099, 1042, 918, 873, 799, 518 cm^{-1}; MS (ESI, + ve) *m*/*z* 318 [(M + Na)$^+$, 100%]; HRMS (ESI, + ve) [M + Na]$^+$ calcd for $C_{16}H_{25}NNaO_4$ 318.1681, found 318.1681.

*3-((3aR,4R,7R,7aS)-4-Ethyl-7-hydroxy-2,2-dimethyl-3a,4,7,7a-tetrahydrobenzo[d][1,3]dioxol-4-yl)propanenitrile (**23**).* A solution of ether **22** (1.77 g, 5.95 mmol) in 2,2-DMP (50 mL) was treated with methanol (5 mL) and then HBr (10 drops of a 48% aqueous solution). The ensuing mixture was stirred at room temperature for 4 h, then diluted with diethyl ether (25 mL), and quenched with $NaHCO_3$ (50 mL of a saturated aqueous solution). The separated aqueous phase was extracted with diethyl ether (2 × 50 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The yellow residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/petroleum spirit elution), and concentration of the relevant fractions (R_f = 0.3) afforded nitrile **23** (1.23 g, 82%) as a clear, pale-yellow oil, $[\alpha]_D$ = −97.3 (*c* = 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (dd, *J* = 10.2 and 2.3 Hz, 1H), 5.38 (dd, *J* = 10.2 and 2.6 Hz, 1H), 4.25−4.20 (complex m, 1H), 4.05−4.00 (complex m, 2H), 2.48−2.19 (complex m, 2H), 1.85 (dd, *J* = 8.7 and 7.5 Hz, 2H), 1.60−1.41 (complex m, 3H), 1.45 (s, 3H), 1.36 (s, 3H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.8, 130.1, 120.4, 108.4, 80.9, 78.3, 69.8, 41.5, 32.4, 31.1, 27.4, 25.2, 13.0, 8.5; IR (KBr) ν_{max} 3444, 2968, 2936, 2247, 1460, 1381, 1242, 1219, 1164, 1067, 1043, 873, 793 cm^{-1}; MS (ESI, + ve) *m*/*z* 274 [(M + Na)$^+$, 100%]; HRMS (ESI, + ve) [M + Na]$^+$ calcd for $C_{14}H_{21}NNaO_3$ 274.1419, found 274.1419.

*3-((3aR,4R,7aR)-4-Ethyl-2,2-dimethyl-7-oxo-3a,4,7,7a-tetrahydrobenzo[d][1,3]dioxol-4-yl)propanenitrile (**24**).* A magnetically stirred solution of nitrile **23** (1.23 g, 4.88 mmol) in dichloromethane (50 mL) maintained at room temperature was treated with Attenburrow MnO_2[36] (4.24 g, 48.80 mmol, 10 equiv). The resulting suspension was stirred for 18 h and then filtered through a pad of diatomaceous earth that was washed with dichloromethane (2 × 50 mL). The combined filtrates were concentrated under reduced pressure, and the brown residue thus obtained was subjected to flash chromatography (silica, 1:10 v/v diethyl ether/dichloromethane elution); concentration of the relevant fractions (R_f = 0.5) afforded enone **24** (1.22 g, quantitative) as a clear, pale-yellow oil, $[\alpha]_D$ = −45.3 (*c* = 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (dd, *J* = 10.4 and 2.3 Hz, 1H), 6.14 (d, *J* = 10.4 Hz, 1H), 4.32 (d, *J* = 4.8 Hz, 1H), 4.22 (dd, *J* = 4.8 and 2.3 Hz, 1H), 2.60 (m, 1H), 2.43 (m, 1H), 2.19−2.07 (complex m, 1H), 2.07−1.97 (complex m, 1H), 1.62 (ABq, *J* = 7.5 Hz, 2H), 1.39 (s, 3H), 1.31 (s, 3H), 0.96 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7, 152.4, 127.8, 119.8, 109.4, 79.7, 74.8, 41.7, 32.1, 31.6, 27.4, 26.0, 12.7, 8.4; IR (KBr) ν_{max} 2929, 2247, 1685, 1460, 1374, 1227, 1164, 1079, 872, 795 cm^{-1}; MS (EI, 70 eV) *m*/*z* 249 (M$^{+\bullet}$, 4%), 234 (71), 192 (50), 162 (60), 100 (100); HRMS (EI) M$^{+\bullet}$ calcd for $C_{14}H_{19}NO_3$ 249.1365, found 249.1367.

*3-((3aR,4R,7aR)-4-Ethyl-6-iodo-2,2-dimethyl-7-oxo-3a,4,7,7a-tetrahydrobenzo[d][1,3]dioxol-4-yl)propanenitrile (**25**).* A solution of enone **24** (1.20 g, 4.81 mmol) in chloroform (10 mL) maintained at room temperature was treated with pyridine (10 mL) and then molecular iodine (4.89 g, 19.25 mmol, 4 equiv). The ensuing mixture was stirred for 24 h, then diluted with dichloromethane (30 mL), and quenched with $Na_2S_2O_3$ (60 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (2 × 50 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow residue thus obtained was subjected to flash chromatography (silica, 1:3 v/v ethyl acetate/petroleum spirit elution), and concentration of the relevant fractions (R_f = 0.5 in 1:1 v/v ethyl acetate/petroleum spirit) afforded iodoenone **25** (1.81 g, quantitative) as a clear, pale-yellow oil, $[\alpha]_D$ = −61.6 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 2.0 Hz, 1H), 4.49 (d, *J* = 4.6 Hz, 1H), 4.27 (dd, *J* = 4.6 and 2.1 Hz, 1H), 2.60 (ddd, *J* = 16.9, 10.1, and 5.9 Hz, 1H), 2.45 (ddd, *J* = 16.9, 10.1, and 5.8 Hz, 1H), 2.16 (ddd, *J* = 14.0, 10.1, and 5.8 Hz, 1H), 2.02 (ddd, *J* = 14.0, 10.1, and 5.8 Hz, 1H), 1.67−1.60 (complex m, 2H), 1.39 (s, 3H), 1.29 (s, 3H), 0.99 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.5, 160.9, 119.4, 110.0, 101.1, 79.7, 73.9, 45.9, 31.8, 31.2, 27.4, 25.9, 12.7, 8.6; IR (KBr) ν_{max} 2984, 2935, 2247, 1694, 1596, 1460, 1383, 1372, 1227, 1080, 871, 785, 739 cm^{-1}; MS (EI, 70 eV) *m*/*z* 375 (M$^{+\bullet}$, 40%), 360 (41), 346 (61), 318 (25), 248 (24), 162 (30), 134 (51), 100 (100), 93 (67); HRMS (EI) M$^{+\bullet}$ calcd for $C_{14}H_{18}INO_3$ 375.0331, found 375.0332.

*3-((3aR,4R,7aR)-4-Ethyl-6-(4-methoxy-2-nitrophenyl)-2,2-dimethyl-7-oxo-3a,4,7,7a-tetrahydrobenzo[d][1,3]dioxol-4-yl)-propanenitrile (**27**).* Iodoenone **25** (1.70 g, 4.53 mmol), Cu powder (2.86 g, 45.30 g.atom, 10 equiv), aryl iodide **26** (1.90 g, 6.80 mmol, 1.5 equiv), CuI (863 mg, 4.53 mmol, 1 equiv) and Pd(dppf)Cl_2•CH_2Cl_2 (367 mg, 0.45 mmol, 0.1 equiv) were added to a flask that was maintained under an atmosphere of nitrogen. DMSO (80 mL) was then added to the mixture and the resulting suspension stirred vigorously at 70 °C for 2 h. The cooled reaction mixture was quenched with NH_4Cl (80 mL of a half-saturated aqueous solution) and extracted with ethyl acetate (4 × 150 mL) using a small amount of brine to break up any emulsion that was encountered. The combined organic phases were dried (Na_2SO_4), filtered, and then concentrated under reduced pressure, and the resulting brown residue was subjected to flash chromatography (silica, 1:3 → 1:1 v/v ethyl acetate/petroleum spirit gradient elution). Concentration of the relevant fractions (R_f = 0.5 in 1:1 v/v ethyl acetate/petroleum spirit) afforded compound **27** (1.67 g, 92%) as a clear, yellow oil, $[\alpha]_D$ = −155.6 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 2.6 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.16 (dd, *J* = 8.4 and 2.6 Hz, 1H), 6.50 (d, *J* = 2.1 Hz, 1H), 4.53 (d, *J* = 4.9 Hz, 1H), 4.32 (dd, *J* = 4.9 and 2.1 Hz, 1H), 3.89 (s, 3H), 2.71−2.61 (complex m, 1H), 2.61−2.52 (complex m, 1H), 2.18 (ddd, *J* = 14.1, 9.2, and 6.4 Hz, 1H), 2.10 (ddd, *J* = 14.1, 9.2, and 6.2 Hz, 1H), 1.78 (dd, *J* = 14.3 and 7.5 Hz, 1H), 1.71 (dd, *J* = 14.3 and 7.5 Hz, 1H), 1.41 (s, 3H), 1.36 (s, 3H), 1.06 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 160.1, 148.7, 147.4, 137.9, 132.5, 122.9, 120.0, 109.5(4), 109.5(0), 79.9, 75.7, 56.0, 41.4, 32.9, 32.5, 27.3, 25.8, 13.1, 8.7; IR (KBr) ν_{max} 2981, 2937, 2246, 1687, 1618, 1532, 1352, 1303, 1270, 1227, 1080, 1047, 874, 816, 789 cm^{-1}; MS (EI, 70

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eV) m/z 400 ($M^{+\bullet}$, 23%), 385 (8), 371 (16), 343 (12), 189 (100); HRMS (EI) $M^{+\bullet}$ calcd for $C_{21}H_{24}N_2O_6$ 400.1634, found 400.1632.

Compound 28. A solution of arylenone **27** (1.10 g, 2.75 mmol) in methanol (100 mL) maintained at room temperature was treated with *p*-TsOH•H_2O (2.37 g, 13.74 mmol, 5 equiv) and freshly prepared Raney cobalt[25] (2.20 g, 200% by weight). The flask containing the suspension thus formed was fitted with a balloon of H_2 and the contents stirred at 40 °C for 18 h. The resulting mixture was cooled and then filtered through a plug of basic alumina that was washed with methanol (3 × 50 mL). The combined filtrates were concentrated under reduced pressure, and the brown residue thus obtained was subjected to flash chromatography (silica, 1:10 v/v methanol/dichloromethane →1:20 v/v ammoniacal methanol/dichloromethane elution). Concentration of the relevant fractions (R_f = 0.65 in 1:10 v/v ammoniacal methanol/dichloromethane) afforded amine **28** (833 mg, 85%) as a clear, pale-yellow oil, $[\alpha]_D$ = +10.4 (c = 0.5, C_6H_6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.61 (d, J = 8.5 Hz, 1H), 6.82 (d, J = 2.2 Hz, 1H), 6.79 (dd, J = 8.5 and 2.2 Hz, 1H), 5.15 (d, J = 5.1 Hz, 1H), 4.37 (dd, J = 5.1 and 1.4 Hz, 1H), 3.85−3.76 (complex m, 2H), 3.80 (s, 3H), 3.19 (d, J = 14.0 Hz, 1H), 2.77 (app. t, J = 12.5 Hz, 1H), 2.19−1.95 (complex m, 2H), 1.72 (m, 1H), 1.62−1.53 (complex m, 1H), 1.41 (s, 3H), 1.39−1.31 (complex m, 1H), 1.29−1.17 (complex m, 1H), 1.16 (s, 3H), 0.86 (t, J = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 137.9, 130.0, 120.9, 120.3, 110.0, 109.7, 94.8, 83.7, 74.8, 70.7, 56.1, 55.7, 46.6, 36.7, 33.9, 31.3, 28.3, 26.7, 24.1, 7.8; IR (KBr) ν_{max} 3400, 2930, 1629, 1462, 1369, 1234, 1202, 1157, 1052, 1013, 807 cm^{-1}; MS (ESI, + ve) m/z 357 [$(M + H)^+$, 100%]; HRMS (ESI, + ve) $[M + H]^+$ calcd for $C_{21}H_{29}N_2O_3$ 357.2178, found 357.2178.

***N*-α-Chloroacetyl Derivative of Compound 28.** A stirred solution of amine **28** (30 mg, 0.08 mmol) in dry dichloromethane (5 mL) maintained at 0 °C under an atmosphere of nitrogen was treated with freshly distilled triethylamine (23 μL, 0.17 mmol, 2 equiv) and freshly distilled α-chloroacetyl chloride (10 μL, 0.13 mmol, 2 equiv). After 1 h the reaction mixture was quenched with $NaHCO_3$ (10 mL of a saturated aqueous solution), and the separated aqueous phase was extracted with dichloromethane (2 × 15 mL). The combined organic phases were dried (Na_2SO_4), filtered, and then concentrated under reduced pressure, and the yellow residue thus obtained was subjected to flash chromatography (silica, 1:3 → 1:1 v/v ethyl acetate/petroleum spirit gradient elution). Concentration of the relevant fractions (R_f = 0.5 in 1:1 v/v ethyl acetate/petroleum spirit) afforded the title amide (18 mg, 49%) as an unstable, yellow oil, $[\alpha]_D$ = −191.2 (c = 0.5, C_6H_6). ^{1}H NMR (400 MHz, C_6D_6) δ 7.49 (d, J = 8.8 Hz, 1H), 7.32 (s, 1H), 6.93 (dd, J = 8.8 and 1.7 Hz, 1H), 6.67 (broad s, 1H), 5.92 (s, 1H), 4.64 (d, J = 7.5 Hz, 1H), 4.10 (d, J = 7.5 Hz, 1H), 3.74 (ABq, J = 11.7 Hz, 2H), 3.50 (s, 3H), 3.46 (s, 1H), 3.07 (d, J = 13.5 Hz, 1H), 2.69 (dd, J = 13.5 and 3.1 Hz, 1H), 1.86−1.65 (complex m, 3H), 1.56−1.45 (complex m, 1H), 1.50 (s, 3H), 1.39−1.26 (complex m, 1H), 1.35 (s, 3H), 1.14 (t, J = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ (mixture of rotamers) 165.7, 157.6, 138.9, 128.6, 120.5, 120.1, 110.9, 110.2, 109.9, 95.6, 79.7, 68.4, 55.3(2), 55.2(9), 50.5, 42.5, 41.6, 40.7, 26.3, 25.9, 25.8, 25.4, 24.9, 21.0, 8.9, 1.4; IR (KBr) ν_{max} 3303, 2935, 1632, 1451, 1381, 1282, 1254, 1209, 1158, 1045, 875, 733 cm^{-1}; MS (EI, 70 eV) m/z 434 and 432 ($M^{+\bullet}$, 15 and 41% respectively), 397 (100), 374 (26), 354 (64); HRMS (EI) $M^{+\bullet}$ calcd for $C_{23}H_{29}{}^{35}ClN_2O_4$ 432.1816, found 432.1816.

Compound 29. A stirred solution of amine **28** (530 mg, 1.49 mmol) in ethanol (200 mL) maintained at room temperature under an atmosphere of nitrogen was treated with K_2CO_3 (2.05 g, 14.86 mmol, 10 equiv) and 2-bromoethanol (1.06 mL, 14.86 mmol, 10 equiv). The ensuing solution was heated under reflux for 18 h, then cooled, and concentrated under reduced pressure to ca. one-eighth of its original volume. The residue thus obtained was diluted with dichloromethane (175 mL) and washed with $NaHCO_3$ (100 mL of a half-saturated solution). The separated aqueous phase was extracted with dichloromethane (2 × 150 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and then concentrated under reduced pressure to yield a yellow oil. Subjection of this material to flash chromatography (silica, 1:10 v/v ammoniacal methanol/dichloromethane elution) and concentration of the relevant fractions (R_f = 0.2) afforded ethanolamine **29** (573 mg, 96%) as a white foam, $[\alpha]_D$ = −38.0 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.45 (d, J = 8.7 Hz, 1H), 6.89 (d, J = 2.1 Hz, 2H), 6.77 (dd, J = 8.7 and 2.1 Hz, 1H), 5.22 (d, J = 6.6 Hz, 1H), 4.33 (d, J = 6.6 Hz, 1H), 3.79 (s, 3H), 3.53−3.44 (complex m, 1H), 3.28 (broad s, 1H), 3.09 (m, 2H), 2.66−2.27 (complex m, 3H), 2.09−1.93 (complex m, 1H), 1.70−1.48 (complex m, 2H), 1.40 (s, 6H), 1.12−0.92 (complex m, 2H), 0.91−0.80 (complex m, 1H), 0.73 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 137.5, 130.9, 122.4, 119.4, 110.5, 109.6, 95.0, 82.0, 69.8, 62.4, 56.7, 55.6, 54.1, 51.8, 41.3, 32.4, 31.7, 27.1, 24.8, 22.4, 8.0 (signal due to one carbon obscured or overlapping); IR (KBr) ν_{max} 3243, 2926, 1628, 1567, 1504, 1460, 1377, 1279, 1263, 1203, 1161, 1054, 1036, 881, 816, 732 cm^{-1}; MS (ESI, + ve) m/z 401 [$(M + H)^+$, 100%]; HRMS (ESI, + ve) $[M + H]^+$ calcd for $C_{23}H_{33}N_2O_4$ 401.2440, found 401.2440.

Compound 31. A stirred solution of compound **29** (100 mg, 0.25 mmol) and freshly distilled Hünig's base (97 μL, 0.75 mmol, 3 equiv) in dry dichloromethane (5 mL) maintained at −5 °C (ice/salt bath) under a nitrogen atmosphere was treated with freshly distilled methanesulfonyl chloride (40 μL, 0.50 mmol, 2 equiv). The ensuing mixture was maintained at −5 °C for 2 h and then quenched with $NaHCO_3$ (10 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (2 × 15 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing clear, yellow, and unstable oil (presumed to contain ester **30**) was dissolved in dry THF (5 mL), and the resulting solution placed under a nitrogen atmosphere. While being maintained at room temperature the solution was treated, in one portion, with *t*-BuOK (112 mg, 1.00, 4 equiv). The ensuing mixture was stirred for 1 h, then diluted with diethyl ether (5 mL), and quenched with water (10 mL). The separated aqueous phase was extracted with diethyl ether (2 × 20 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and then concentrated under reduced pressure to yield a yellow oil. Subjection of this material to flash chromatography (silica, 1:20 v/v methanol/dichloromethane elution) and concentration of the relevant fractions (R_f = 0.4) afforded isoindole **31** (88 mg, 92%) as a white foam, $[\alpha]_D$ = −168.8 (c = 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.2 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 6.78 (dd, J = 8.2 and 2.4 Hz, 1H), 5.27 (d, J = 8.0 Hz, 1H), 4.44 (dd, J = 8.0 and 2.0 Hz, 1H), 3.84 (s, 3H), 3.18−3.10 (complex m, 2H), 2.88 (m, 1H), 2.51−2.30 (complex m, 3H), 2.09 (m, 1H), 1.83 (dd, J = 14.2 and 5.1 Hz, 1H), 1.63 (s, 3H), 1.61−1.56 (complex m, 2H), 1.39 (s, 3H), 1.12 (td, J = 13.6 and 5.8 Hz, 1H), 0.55−0.41 (complex m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.9, 159.6, 154.3, 140.5, 121.4, 112.5, 111.1, 106.9, 85.1, 78.9, 75.7, 60.1, 55.5, 55.1, 52.1, 38.0, 34.9, 31.5, 28.9, 24.9, 24.2, 23.5, 7.3; IR (KBr) ν_{max} 2957, 2929, 2770, 2715, 1617, 1590, 1577, 1481, 1441, 1376, 1369, 1321, 1277, 1261, 1209, 1146, 1049, 879, 815 cm^{-1}; MS (ESI, + ve) m/z 383 [$(M + H)^+$, 100%]; HRMS (ESI, + ve) $[M + H]^+$ calcd for $C_{23}H_{31}N_2O_3$ 383.2335, found 383.2336.

Compound 8. A vigorously stirred solution of isoindole **31** (20 mg, 0.05 mmol) in acetic acid/acetonitrile (5 mL of a 1:10 v/v mixture) maintained at room temperature was treated with formaldehyde (2.5 mL of a 37% aqueous solution). The resulting slurry was treated, in small portions, over 1 h, with $NaBH_3CN$ (30 mg, 0.25 mmol, 10 equiv). After a further 1 h the reaction mixture was treated with brine/Na_2CO_3 (10 mL of a 1:1 v/v mixture of saturated solutions), and the separated aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried (Na_2SO_4), filtered, and then concentrated under reduced pressure to yield a milky residue that was subjected to flash chromatography (silica, 1:20 v/v ammoniacal methanol/dichloromethane elution). Concentration of the relevant fractions (R_f = 0.5) afforded indoline **8** (18 mg, 89%) as a white foam, $[\alpha]_D$ = +48.8 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, J = 8.1 Hz, 1H), 6.25 (dd, J = 8.1 and 2.3 Hz, 1H), 6.02 (d, J = 2.3 1H), 4.53 (d, J = 7.4, Hz, 1H), 4.15−4.10 (complex m, 1H), 3.77 (s, 3H), 3.38 (d, J = 2.6 Hz, 1H), 3.08−3.01 (complex m, 2H), 2.83 (s, 3H), 2.36−2.21 (complex m, 1H), 2.15−2.05 (complex m, 2H), 2.03−1.94 (complex m, 1H), 1.90−1.73

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(complex m, 3H), 1.52 (s, 3H), 1.44−1.36 (complex m, 1H), 1.34 (s, 3H), 1.23−1.01 (complex m, 3H), 0.49 (t, J = 7.4 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 152.3, 123.1, 107.6, 103.3, 94.9, 92.3, 78.6, 75.5, 74.4, 74.3, 55.3, 54.8, 53.7, 49.6, 44.1, 36.4, 35.0, 31.9, 30.2, 26.1, 24.5, 23.3, 7.5; IR (KBr) ν_{max} 2930, 1618, 1496, 1456, 1375, 1263, 1224, 1172, 1089, 1055, 899 cm^{-1}; MS (EI, 70 eV) m/z 398 ($M^{+\bullet}$, 54%), 262 (35), 124 (100); HRMS (EI) $M^{+\bullet}$ calcd for $C_{24}H_{34}N_2O_3$ 398.2569, found 398.2571.

Compound 32. A magnetically stirred solution of isoindole **31** (20 mg, 0.05 mmol) in diethyl ether (4 mL) maintained under a nitrogen atmosphere was cooled to −78 °C and then treated with *t*-BuLi (67 μL of a 1.5 M solution, 0.10 mmol, 2 equiv). After 1 h the reaction mixture was treated with freshly distilled Mander's reagent[31] (7 μL, 0.08 mmol, 1.5 equiv), and the resulting mixture was allowed to stir at −78 °C for a further 0.25 h and then was quenched with $NaHCO_3$ (10 mL of a saturated aqueous solution). The separated aqueous phase was extracted with diethyl ether (2 × 20 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The clear, yellow oil thus obtained was submitted to flash chromatography (silica, 1:20 v/v methanol/dichloromethane → 1:20 v/v ammoniacal methanol/dichloromethane gradient elution), and concentration of the relevant fractions (R_f = 0.6 in 1:20 v/v ammoniacal methanol/dichloromethane) afforded carbamate **32** (16 mg, 70%) as a white foam, $[\alpha]_D$ = −29.2 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3OD) δ 7.29 (broad s, 1H), 7.11 (d, J = 8.3 Hz, 1H), 6.60 (dd, J = 8.3 and 2.4 Hz, 1H), 4.36 (d, J = 5.2 Hz, 1H), 4.04 (broad s, 2H), 3.83 (s, 3H), 3.78 (s, 3H), 3.11 (broad s, 2H), 2.43−2.16 (complex m, 3H), 2.15−1.95 (complex m, 2H), 1.89 (d, J = 14.2 Hz, 1H), 1.67−1.47 (complex m, 2H), 1.58 (s, 3H), 1.39−1.31 (complex m, 1H), 1.35 (s, 3H), 1.15−1.04 (complex m, 2H), 0.73 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 161.3, 156.0, 142.9, 131.8, 124.3, 110.3, 110.1, 104.0, 80.7, 79.7, 72.0, 71.6, 55.9, 54.7, 53.8, 53.3, 53.2, 42.1, 38.0, 33.8, 33.0, 28.0, 26.1, 24.4, 7.8; IR (KBr) ν_{max} 2929, 2779, 1713, 1614, 1499, 1454, 1386, 1312, 1250, 1212, 1158, 1065, 861 cm^{-1}; MS (EI, 70 eV) m/z 442 ($M^{+\bullet}$, 21%), 367 (8), 342 (7), 262 (15), 124 (100); HRMS (EI) $M^{+\bullet}$ calcd $C_{25}H_{34}N_2O_5$ 442.2468, found 442.2463.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02788.

^{1}H and ^{13}C NMR spectra data for compounds **11**, **13**, **14**, **18**, **19**, product of reduction of **19**, **20**−**28**, *N*-α-chloroacetyl derivative of **28**, **29**, **31**, **8**, **32** (PDF)

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Notes

The authors declare no competing financial interest.

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