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# Total Synthesis of (−)-Colchicine by an Oxyallyl [4+3] Cycloaddition[1]

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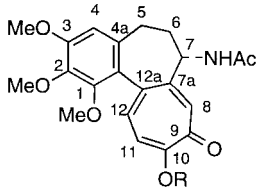
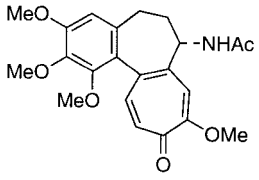
**Abstract**—An enantioselective synthesis of (−)-colchicine, free from isocolchicine, is delineated and features tandem application of the intramolecular Diels–Alder reaction of acetylene-tethered oxazoles and the [4+3] cycloaddition of oxyallyls. This work underscores the synthetic utility of little explored α-alkoxy substituted oxyallyls. 

## Introduction

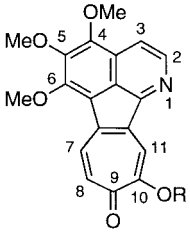
Colchicine (**1**), the principal constituent of the plant *Colchicum autumnale*, belongs to a growing class of naturally occurring tropoloisoquinoline alkaloids which include grandirubrine (**4**), isoimerubrine (**5**), imerubrine (**6**), etc. These structurally related alkaloids exhibit interesting biological properties in arresting cell division during mitosis.[2,3] The antimitotic properties of **1** arise from its binding to tubulin and interference with microtubule-dependent cell functions. The highly selective binding of **1** to tubulin has been attributed to its counterclockwise helical (a*S*)-configuration and conformation of the biaryl system.[2c,4] Although its high toxicity has precluded clinical development as a potential antitumor agent, it remains in use for the treatment of gout and also as a useful biochemical probe. Despite a deceptively simple structure, **1** poses considerable synthetic challenges, which are in part due to the paucity of general methods for preparing the tropolone ring. An unusually large number of synthetic studies have been undertaken during the past four decades, culminating in several elegant total syntheses of **1**.[5,6] Many previous syntheses have relied on the bromination-ammonolysis sequence developed initially by Eschenmoser[5a] and van Tamelen[5b] to introduce the C-7 acetamide group in deacetamidoisocolchicine, which proved to be better suited for the requisite allylic bromination than deacetamidocolchicine.[5] Moreover, all of the previous syntheses,[5,6] with the sole exception of Banwell,[6d] have resorted to the penultimate intermediacy of colchiceine (**2**) or deacetylcolchiceine. Consequently, they suffer from lack of regiocontrol in the final methylation which affords equal amounts of **1** and isocolchicine (**3**), albeit that the latter methyl ether **3** could be recycled by ammonolysis and treatment with alkali. Herein detailed is a regiocontrolled, enantioselective synthesis of (−)-colchicine (**1**), which should also provide a unified approach to other structurally related tropoloisoquinoline alkaloids, such as **4**, **5**, and **6**.[7]



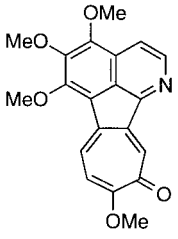

colchicine (**1**): R = Me
colchiceine (**2**): R = H




isocolchicine (**3**)




grandirubrine (**4**): R = H
isoimerubrine (**5**): R = Me




imerubrine (**6**)

## Results and Discussion

### Preparation of furan (9) by Diels–Alder reactions of acetylene oxazoles

A key approach was predicated on our ongoing applications of oxyallyl [4+3] cycloaddition reactions in natural product synthesis.[1,8,9] Particularly appealing was a little-explored

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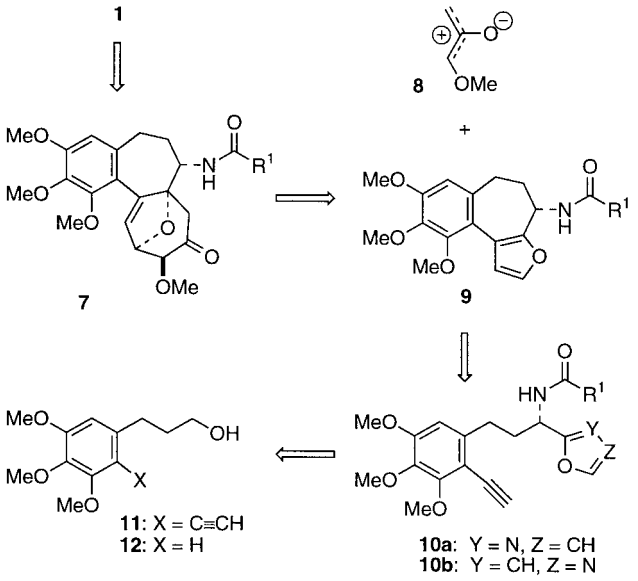
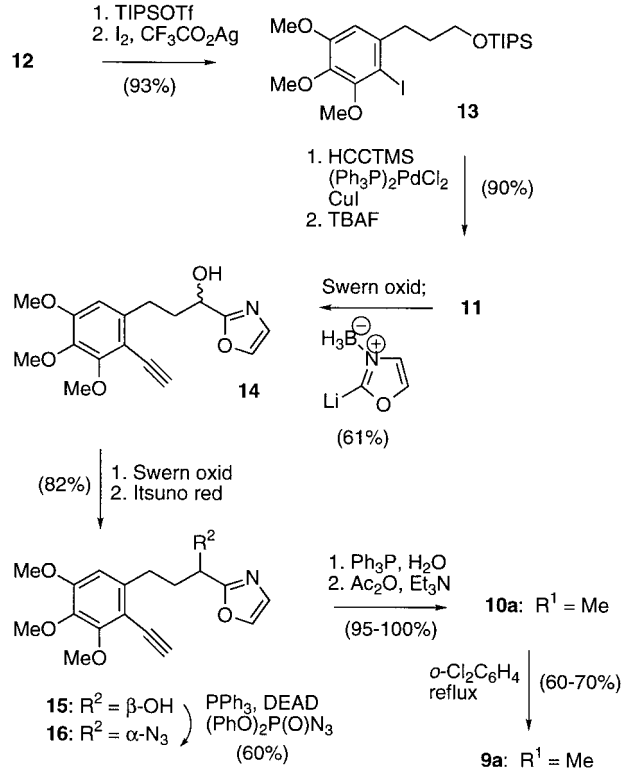
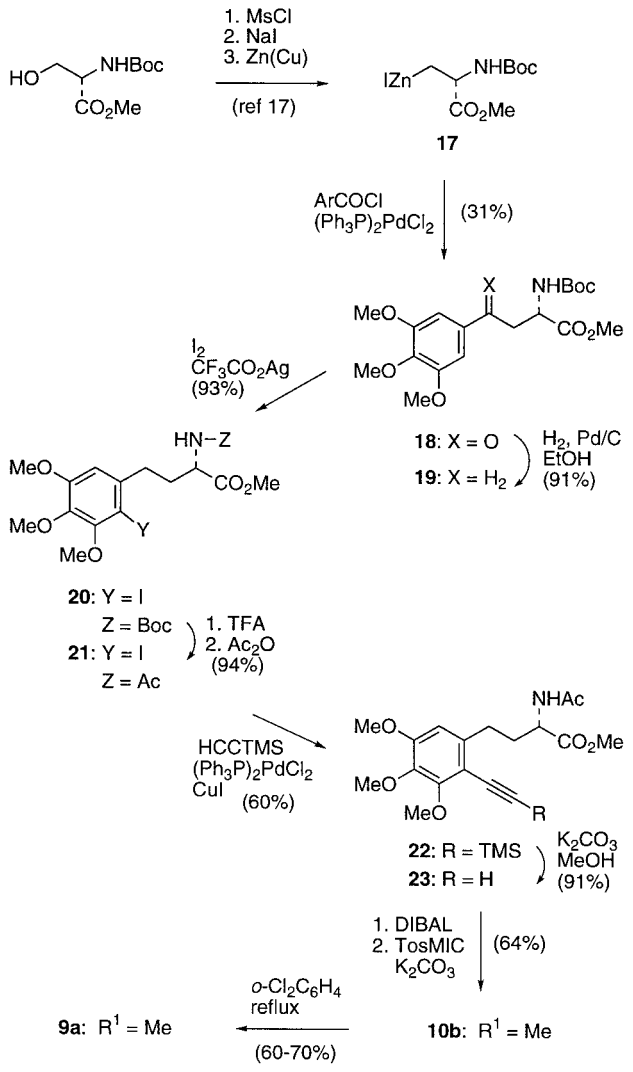



Scheme 1.

variant of utilizing α-heteroatom substituted oxyallyls;[10,11] while a few methods for their generation are known, to our knowledge no synthetic application has been explored. Thus, the [4+3] cycloaddition of α-methoxy substituted oxyallyl **8** to furan **9** was envisaged to provide a unique solution for the (stereo- and) regiocontrolled construction of the cycloadduct **7** (Scheme 1). Subsequent double elimination would then give **1**, free from **3**, by precluding the intermediacy of colchiceine (**2**). The requisite tricyclic furan **9** should be available by the intramolecular Diels–Alder



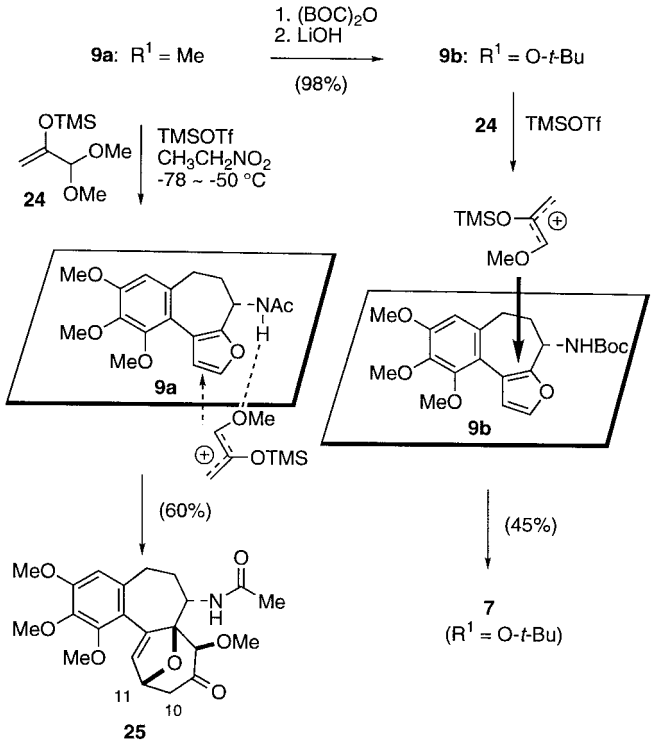

Scheme 2.




Scheme 3.

reaction of the acetylene-tethered oxazole **10**, as the cognate preparation of fused-ring furans from acetylene-tethered oxazoles has been amply demonstrated by Jacobi and coworkers.[12] Finally, **10** would in turn be prepared from **11** via the known alcohol **12**. Sequential applications of the intramolecular Diels–Alder reaction of an acetylene-tethered oxazole, the [4+3] cycloaddition of an α-methoxy substituted oxyallyl, and double elimination of the resulting cycloadduct would present a unified approach to structurally similar members of the tropoloisoquinoline family, as well as opportunities for the preparation of tropolone congeners potentially possessing comparable biological activity, yet devoid of toxicity.

The acetylene alcohol **11** was first prepared from alcohol **12** in 84% overall yield by means of the Sonogashira coupling of aryl iodide **13**: 1. TIPSOTf, 2,6-lutidine; 2. $I_2$, $CF_3CO_2Ag$, $CHCl_3$; 3. HC≡CTMS, $Et_2NH$, $(Ph_3P)_2PdCl_2$, CuI, DMSO; 4. *n*-$Bu_4NF$, THF (Scheme 2). Swern oxidation, followed by addition of the anion prepared in situ from the oxazole-borane complex using the method of Vedejs, afforded oxazole **14**.[13a] It is noteworthy that Vedejs' procedure provides a practical solution for functionalization




**Scheme 4.**

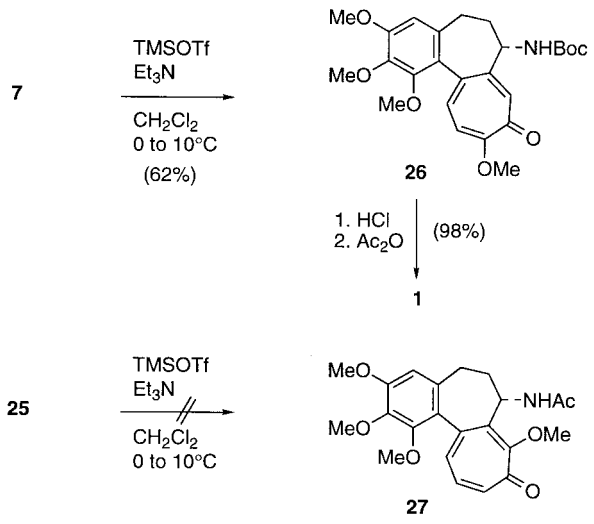
of oxazoles at C-2 without the complications due to facile ring opening of 2-lithiooxazoles. (Parent) oxazole is no longer commercially available, but may be prepared by the method of Brederick and Bangert.[13a,b] However, we have found that oxazole can be prepared most conveniently, on a multigram scale, by condensation of TosMIC with formaldehyde and subsequent elimination of *p*-toluenesulfinic acid by potassium hydroxide (see the Experimental section for details).

Toward the enantioselective preparation of the C-7 acetamide group, the (*R*)-alcohol **15** was next secured by Itsuno reduction using an (*S*)-valinol derivative in 82% yield.[14,15] Subsequent conversion of **15** to azide **16** was achieved (60%) with inversion of configuration by a Mitsunobu reaction.[16] Reduction of the azide functionality and acetylation then afforded acetamide **10a** (where $R^1$=Me) in nearly quantitative yield. It was gratifying that thermolysis (*o*-dichlorobenzene, reflux) provided the furan **9a** (where $R^1$=Me), $\alpha_D$=−14.8° (*c* 1.2, $CHCl_3$), in 60–70% yield and with little racemization: enantiomeric excess was estimated to be 85–90% ee by the NMR studies with the chiral shift reagent, Eu(hfc)$_3$. Upon addition of Eu(hfc)$_3$, for example, independently prepared, racemic furan **9a** gave separate pairs of signals for the *N*-acetyl methyl protons.

An alternate preparation of the key intermediate **9a** was achieved by employing an enantiomerically pure α-amino acid as the chiral source instead of enantioselective reduction of a prochiral ketone. Starting from *N*-(*tert*-butoxycarbonyl)-L-serine methyl ester, the functionalized zinc reagent **17** was prepared via protected L-iodoalanine by the procedure of Jackson (Scheme 3).[17] Treatment of **17** with 3,4,5-trimethoxybenzoyl chloride under the conditions described by Jackson[17] [i.e. in the presence of catalytic bis(triphenylphosphine)palladium dichloride in an ultrasonic cleaning bath] afforded 4-oxo-α-amino acid **18** in only 31% yield. A higher yield (52–65%) was obtained in coupling with unsubstituted benzoyl chloride (when Ar=Ph). In any event, catalytic hydrogenation of **18** gave enantiomerically pure Boc-homoarylalanine **19** in 91% yield. Following iodination (93%), the Boc protecting group was then replaced by the acetyl group to furnish acetamide **21** in 94% yield. As previously described for the preparation of **11**, Sonogashira coupling of the aryl iodide **21** and subsequent desilylation of **22** afforded acetylene **23** in 55% overall yield. Reduction of its ester moiety with DIBAL-H, followed by treatment with TosMIC according to the procedure of van Leusen,[18] provided oxazole **10b** (where $R^1$=Me) in 64% yield. Finally, thermolysis (*o*-dichlorobenzene, reflux) provided enantiomerically pure furan **9a** (where $R^1$=Me), $[\alpha]_D^{23}$=−15.9° (*c* 3.4, $CHCl_3$), in 62–70% yield. Interestingly, 'bis-heteroannulation' of **10b** (40 h) was found to proceed faster than that of the isomeric oxazole **10a** (66 h), although comparable yields were obtained in both processes. It is also pertinent to note that the Boc protecting group (i.e., $R^1$=*O*-*t*-Bu in **10**) could not be used for the 'bis-heteroannulation', since it suffered concomitant thermal elimination.

## Oxyallyl [4+3] cycloadditions

The key [4+3] cycloaddition of the furan **9a** ($R^1$=Me) was carried out by adaptation of Albizati's procedure which involves in situ generation (with TMSOTf) of α-methoxy trimethylsiloxyallyl cation (e.g. **8**) from the trimethylsilyl enol ether **24** of pyruvic aldehyde dimethyl acetal (Scheme 4).[10c] We were surprised that the undesired regioisomer **25** was isolated as the sole product (60% yield based on 50%




**Scheme 5.**

conversion of the starting material). Although the regiochemistry was unequivocally established by the splitting pattern of the methylene protons at C-10 (colchicine numbering), the *exo* proton of which is coupled to the bridgehead proton at C-11 with the characteristic vicinal coupling constant ($J$=5.0 Hz),[19] the stereochemistry could not be determined. While speculative at this juncture, it is tempting to hypothesize that hydrogen bonding between the acetamide N–H proton and the methoxy moiety of the siloxyallyl cation or oxyallyl species might be involved in the [4+3] cycloaddition of **9a.** As depicted in Scheme 4, the W-shaped oxyallyl could then approach from the α-face of the furan, i.e. *syn* to the acetamide functionality, in an atypical, 'extended' (*exo*-like) mode.[20] This postulate on hydrogen bonding prompted us to investigate the cycloaddition of the *N*-methyl acetamide (structure not shown) which was readily available by sequential treatment of **9a** with NaH and MeI. Surprisingly, no cycloadduct was obtained under the identical reaction conditions; instead the unreacted *N*-methyl acetamide was recovered. Use of a different amine protecting group which serves as a poor hydrogen bond donor in the cycloaddition step was next considered, and the Boc derivative **9b** ($R^1$=*O*-*t*-Bu) was prepared from **9a** by standard methods.[21] The desired cycloadduct **7** ($R^1$=*O*-*t*-Bu) was indeed obtained as a single diastereomer in 45% yield (based on 50% conversion of the starting material). Regiochemistry was firmly established by the splitting pattern (an AB quartet) of the methylene protons at C-8 (colchicine numbering), and the stereochemistry was tentatively assigned by analogy to Albizati's previous examples involving simple furans,[10c] which are consistent with the approach of the W-shaped oxyallyl cation from the less hindered, β-face of the furan in a 'compact' (*endo*-like) mode. Particularly remarkable is the divergence in the regioselectivity of the [4+3] cycloadditions of **9a** and **9b**. While elucidation of the origin of the regio- and stereoselective cycloadditions of **9a**,**b** must await further study (including the unequivocal stereochemical determination of **7** and **25**), these results suggest a general method for highly diastereoselective [4+3] cycloadditions directed by the influence of an adjacent substituent.[10,11,20]

## Double elimination of the oxa bridge

By adaptation of a slightly modified procedure of Föhlisch and Mann involving treatment of **7** with excess amounts of TMSOTf and $Et_3N$ in $CH_2Cl_2$,[22,23] a fully assembled colchicine derivative, 2-methoxytropone **26**, was prepared (62%) in one step (Scheme 5). Typically, 10 equiv of $Et_3N$ and 5 equiv of TMSOTf were added at 0–10°C to ensure reproducible yields. In contrast, **25** proved resistant toward elimination of the ether bridge under the identical conditions and was recovered unchanged. The striking failure of **25** to undergo ring opening might be a consequence of the axial orientation of the methoxy group at C-8, which would impede the requisite enolization, an obligatory step for double elimination of the oxa bridge. Finally, the Boc amino protecting group of **26** was replaced by the *N*-acetyl group to complete a total synthesis of (−)-**1** in ~90% ee.[24] The synthetic substance was found to be identical with an authentic sample of natural colchicine: mp 153–154°C; $[\alpha]_D$=−143.5° (*c* 0.4, $CHCl_3$) {$[\alpha]_D$=−161.4° (*c* 0.43, $CHCl_3$) for natural colchicine}.

## Conclusion

The [4+3] cycloaddition of an α-alkoxy substituted oxyallyl cation to a suitably functionalized furan, followed by double elimination of the oxa bridge, provides an efficient, regioselective entry to colchicine (**1**). Moreover, tandem application of the intramolecular Diels–Alder reaction of acetylene-tethered oxazoles and the [4+3] cycloaddition of oxyallyls is anticipated to offer a unified approach to structurally related tropoloisoquinoline alkaloids **4**–**6**, as well as a stereocontrolled route to bioactive natural products containing medium-sized carbocycles and heterocycles.

## Experimental[25,26]

**5-(3-Triisopropylsiloxypropyl)-4-iodo-1,2,3-trimethoxybenzene (13).** To a solution of alcohol **12** (8.337 g, 36.85 mmol) and 2,6-lutidine (20.1 g, 0.19 mol) in $CH_2Cl_2$ (40 mL) was added dropwise at 0°C triisopropylsilyl trifluoromethanesulfonate (13.8 g, 45 mmol). The mixture was stirred for 5 h at room temperature and quenched with water (70 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2×50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography (20:1 hexane–EtOAc) provided the silyl ether (13.82 g, 98%) as a colorless oil: IR (film) 1593, 1510, 1465 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 6.42 (s, 2H), 3.84 (s, 6H), 3.82 (s, 3H), 3.72 (t, $J$=6.2 Hz, 2H), 2.66 (t, $J$=7.7 Hz, 2H), 1.89–1.81 (m, 2H), 1.07 (s, 21H); $^{13}C$ NMR (90 MHz, $CDCl_3$) δ 153.0, 138.1, 136.0, 105.4, 62.4, 60.8, 56.0, 34.6, 32.4, 18.0, 12.0; HRMS ($M^+$) calcd for $C_{21}H_{38}O_4Si$ 382.2539, found 382.2565.

To a stirred suspension of the TIPS ether (15.25 g, 39.86 mmol), sodium bicarbonate (6.7 g, 80 mmol), and silver trifluoroacetate (8.8 g, 40 mmol) in anhydrous $CHCl_3$ (80 mL) was added dropwise iodine (10.1 g, 40 mmol) in $CHCl_3$ (300 mL) over a period of 2 h at 0°C.

After stirring an additional 1 h, the mixture was filtered and the precipitated silver iodide was washed with chloroform (100 mL). The solvent was removed in vacuo. Purification by column chromatography (50:1 hexane–EtOAc) afforded the iodide **13** (19.23 g, 95%) as a colorless oil: IR (film) 1568, 1484 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 6.66 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.76 (t, $J$=6.3 Hz, 2H), 2.82 (m, 2H), 1.89–1.79 (m, 2H), 1.07 (s, 21H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 153.4, 153.0, 140.6, 140.1, 108.8, 88.0, 62.4, 60.9, 60.6, 56.0, 37.4, 33.3, 18.0, 12.0; HRMS ($M^+$) calcd for $C_{21}H_{37}O_4ISi$ 508.1506, found 508.1514.

**3-(2-Ethynyl-3,4,5-trimethoxyphenyl)propan-1-ol (11).** To a mixture of compound **13** (1.6 g, 3.15 mmol), trimethylsilylacetylene (1.5 g, 15.7 mmol), and diethylamine (5 mL) in DMSO (20 mL) were added bis[triphenylphosphine]-palladium dichloride (44 mg, 0.06 mmol) and copper(I) iodide (24 mg, 0.13 mmol). After the reaction mixture had been stirred at 90°C for 20 h in a sealed tube, it was cooled to room temperature, poured into water (100 mL), and extracted with $CH_2Cl_2$ (3×50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (40:1 hexane–EtOAc) afforded the coupling product (1.393 g, 92%) as a colorless oil: IR (film) 2154, 1601, 1501, 1463 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 6.52 (s, 1H), 3.95 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.72 (t, $J$=6.4 Hz, 2H), 2.80 (t, $J$=7.7 Hz, 2H), 1.92–1.84 (m, 2H), 1.07 (s, 21H), 0.24 (s, 9H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 155.2, 153.6, 141.8, 139.9, 109.9, 108.1, 100.8, 99.7, 62.8, 61.1, 61.0, 55.9, 33.4, 31.1, 18.0, 12.0, 0.0; HRMS ($M^+$) calcd for $C_{26}H_{46}O_4Si_2$ 478.2935, found 478.2925.

The TMS-protected alkyne (12.93 g, 27 mmol) in THF (50 mL) was treated at 0°C with $n$-$Bu_4NF$ (81 mL of a 1.0 M solution in THF). After the resulting mixture had been stirred for 7 h at room temperature, it was quenched with aqueous saturated $NH_4Cl$ solution and extracted with EtOAc (2×100 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography (1:1 hexane–EtOAc) provided compound **11** (6.620 g, 98%) as a colorless oil: IR (film) 3414, 3284, 2105 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 6.52 (s, 1H), 3.95 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.66 (t, $J$=6.3 Hz, 2H), 3.39 (s, 1H), 2.82 (t, $J$=7.6 Hz, 2H), 1.93–1.85 (m, 2H), 1.68 (br s, 1H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 155.4, 154.0, 141.3, 140.0, 108.7, 107.9, 83.4, 78.4, 62.0, 61.2, 61.0, 55.9, 33.4, 30.7; HRMS ($M^+$) calcd for $C_{14}H_{18}O_4$ 250.1205, found 250.1180.

## Preparation of oxazole

To a solution of paraformaldehyde (0.75 g, 25 mmol) in DMSO (60 mL) and water (30 mL) were added TosMIC (4.88 g, 25 mmol) and $K_2CO_3$ (3.5 g, 25 mmol). The mixture was stirred at room temperature for 5 h and poured into $CH_2Cl_2$ (100 mL) and water (100 mL). The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2×50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to give 4-tosyloxazoline (4.08 g). To a solution of crude 4-tosyloxazoline in ethylene glycol (10 mL) was added KOH (1.0 g, 18 mmol) in ethylene glycol (10 mL). After the mixture had been stirred at room temperature for 5 h, careful distillation afforded 0.62 g of oxazole in 36% (unoptimized) overall yield.

**3-(2-Ethynyl-3,4,5-trimethoxyphenyl)-1-(2,5-oxazolyl)-propan-1-ol (14).** To a solution of oxalyl chloride (2.4 g, 18.5 mmol) in $CH_2Cl_2$ (30 mL) was added dropwise at −78°C a solution of DMSO (2.5 g, 32 mmol) in $CH_2Cl_2$ (30 mL). After the mixture had been stirred for 30 min, a solution of alcohol **11** (1.58 g, 6.33 mmol) in $CH_2Cl_2$ (15 mL) was added dropwise during 15 min at −78°C. The reaction mixture was stirred for an additional 30 min, and $Et_3N$ (4.480 g, 44.32 mmol) was added dropwise. The mixture was then allowed to warm to 0°C. It was poured into $CH_2Cl_2$ (50 mL) and water (75 mL). The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (4:1 hexane–EtOAc) to give the aldehyde (1.51 g, 96%) as a colorless oil: IR (film) 3298, 3064, 2108, 1728, 1604 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 9.82 (br t, $J$= 1.0 Hz, 1H), 6.53 (s, 1H), 3.96 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.41 (s, 1H), 3.05 (t, $J$=7.5 Hz, 2H), 2.81 (dt, $J$=7.5, 1.0 Hz); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 201.4, 155.6, 154.1, 140.4, 139.8, 108.7, 108.2, 84.0, 77.9, 61.2, 61.0, 56.0, 44.3, 27.2; HRMS ($M^+$) calcd for $C_{14}H_{16}O_4$ 248.1049, found 248.1031.

A solution of oxazole (95 mg, 1.37 mmol) in THF (5 mL) at room temperature was treated with $BH_3$–THF (1.4 mL of a 1.0 M solution in THF). After 1 h, the solution was cooled to −78°C and $t$-BuLi (0.9 mL of a 1.7 M solution in pentane) was added dropwise. After the mixture had been stirred for 40 min, the aldehyde (0.34 g, 1.37 mmol) in THF (1.5 mL) was added at −78°C. The reaction mixture was then stirred for 3 h, followed by addition of 8 mL of 5% HOAc in ethanol. The cooling bath was removed, and the mixture was stirred for 22 h at room temperature to cleave the borane complex. The mixture was poured into $Et_2O$ (20 mL) and water (25 mL). The layers were separated, and the aqueous layer was extracted with $Et_2O$ (4×20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (2:1 hexane–EtOAc) afforded **14** (0.28 g, 64%) as a colorless oil: IR (film) 3403, 3284, 2101, 1598, 1497 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.62 (s, 1H), 7.08 (s, 1H), 6.54 (s, 1H), 4.85–4.82 (m, 1H), 3.96 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.37 (s, 1H), 2.97 (br s, 1H), 2.95–2.84 (m, 2H), 2.34–2.15 (m, 2H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 165.5, 155.6, 154.1, 140.5, 140.2, 138.9, 126.8, 108.8, 108.2, 83.6, 78.2, 67.0, 61.3, 61.0, 56.0, 36.0, 30.1; HRMS ($M^+$) calcd for $C_{17}H_{19}NO_5$ 317.1263, found 317.1248.

**(1*R*)-3-(2-Ethynyl-3,4,5-trimethoxyphenyl)-1-(2,5-oxazolyl)-propan-1-ol (15).** To a solution of oxalyl chloride (0.42 g, 3.3 mmol) in $CH_2Cl_2$ (5 mL) was added dropwise at −78°C a solution of DMSO (0.36 g, 4.6 mmol) in $CH_2Cl_2$ (5 mL). After the mixture had been stirred for 30 min, a solution of alcohol **14** (0.21 g, 0.66 mmol) in $CH_2Cl_2$ (5 mL) was added dropwise during 10 min. The reaction mixture was stirred for 30 min at −78°C, followed by dropwise addition of $Et_3N$

(0.67 g, 6.6 mmol). The mixture was then allowed to warm to 0°C. The mixture was poured into $CH_2Cl_2$ (15 mL) and water (15 mL). The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2×15 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (3:2 hexane–EtOAc) afforded the ketone (0.20 g, 96%) as a colorless oil: IR (film) 3418, 2136, 1734, 1658 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.81 (s, 1H), 7.32 (s, 1H), 6.61 (s, 1H), 3.96 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.46 (t, $J$=7.5 Hz, 2H), 3.40 (s, 1H), 3.18 (t, $J$=7.5 Hz, 2H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 187.3, 157.9, 155.6, 154.0, 141.5, 140.4, 139.8, 129.1, 108.9, 108.5, 84.1, 77.9, 61.3, 61.0, 56.0, 39.7, 28.5; HRMS ($M^+$) calcd for $C_{17}H_{17}NO_5$ 315.1107, found 315.1079.

A solution of $BH_3$–THF (9.3 mL of a 1.0 M solution in THF) was added dropwise to a stirred solution of (*S*)-(−)-2-amino-3-methyl-1,1-diphenylbutan-1-ol (1.18 g, 4.6 mmol) in THF (7 mL) at −78°C during 20 min. The reaction mixture was slowly warmed to 23°C and stirred for an additional 9 h. A solution of the ketone (1.14 g, 3.62 mmol) in THF (5 mL) was then added dropwise over 10 min. The resulting mixture was stirred at 23°C for 6 h and poured into $Et_2O$ (30 mL) and water (30 mL). The layers were separated, and the aqueous layer was extracted with $Et_2O$ (3×30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (1:1 hexane–EtOAc) afforded alcohol **15** (1.0 g, 85%) as a colorless oil: $[\alpha]_D$=−18.9° (*c* 1.40, $CHCl_3$); IR (film) 3403, 3284, 2101, 1598, 1497 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.62 (s, 1H), 7.08 (s, 1H), 6.54 (s, 1H), 4.85–4.82 (m, 1H), 3.96 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.37 (s, 1H), 2.97 (br s, 1H), 2.95–2.84 (m, 2H), 2.34–2.15 (m, 2H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 165.5, 155.6, 154.1, 140.5, 140.2, 138.9, 126.8, 108.8, 108.2, 83.6, 78.2, 67.0, 61.3, 61.0, 56.0, 36.0, 30.1; HRMS ($M^+$) calcd for $C_{17}H_{19}NO_5$ 317.1263, found 317.1248.

**5-[(3*S*)-3-Azido-3-(2,5-oxazolyl)propyl]-4-ethynyl-1,2,3-trimethoxybenzene (16).** Diphenylphosphoryl azide (0.69 g, 2.5 mmol) was added dropwise at room temperature during 20 min to a suspension of **15** (0.75 g, 2.36 mmol), triphenylphosphine (0.65 g, 2.5 mmol), and diisopropylazodicarboxylate (0.5 g, 2.5 mmol) in anhydrous THF (10 mL). The reaction mixture was stirred for 12 h at room temperature and concentrated in vacuo. Purification by column chromatography (3:1 hexane–EtOAc) afforded azide **16** (0.49 g, 60%) as a colorless oil: $[\alpha]_D$=−33.6° (*c* 0.14, $CHCl_3$); IR (film) 3312, 2108, 1500 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.67 (s, 1H), 7.14 (s, 1H), 6.51 (s, 1H), 4.49 (dd, $J$=8.4, 6.2 Hz, 1H), 3.96 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.38 (s, 1H), 2.98–2.79 (m, 2H), 2.39–2.24 (m, 2H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 161.7, 155.7, 154.1, 140.5, 139.5, 139.4, 127.4, 108.9, 108.2, 83.8, 77.9, 61.3, 61.0, 57.4, 56.0, 32.8, 30.9; HRMS ($M^+$) calcd for $C_{17}H_{18}N_4O_4$ 342.1328, found 342.1319.

**(*S*)-*N*-Acetyl-3-(2-ethynyl-3,4,5-trimethoxyphenyl)-1-(2-oxazolyl)-propylamine (10a).** A mixture of **16** (0.81 g, 2.37 mmol) and triphenylphosphine (1.0 g, 3.9 mmol) in THF (10 mL) containing water (0.09 g, 5 mmol) was stirred at room temperature for 50 h and concentrated in vacuo. Purification by column chromatography (10:1 $CH_2Cl_2$–MeOH) afforded the amine (0.710 g, 95%) as a colorless oil: $[\alpha]_D$=−10.4° (*c* 0.36, $CHCl_3$); IR (film) 3377, 3289, 2101, 1598, 1563 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.60 (s, 1H), 7.06 (s, 1H), 6.55 (s, 1H), 4.12 (t, $J$=6.5 Hz, 1H), 3.94 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.35 (s, 1H), 2.92–2.78 (m, 2H), 2.60 (br s, 2H), 2.30–2.13 (m, 2H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 167.0, 155.5, 154.0, 140.6, 140.2, 138.7, 126.8, 108.7, 108.2, 83.6, 78.1, 61.2, 61.0, 56.0, 49.5, 36.4, 30.8; HRMS ($M^+$) calcd for $C_{17}H_{20}N_2O_4$ 316.1423, found 316.1395.

A mixture of the amine (0.39 g, 1.23 mmol), acetic anhydride (0.2 g, 1.9 mmol), triethylamine (0.28 mL, 1.9 mmol), and DMAP (0.01 g, 0.1 mmol) in $Et_2O$ (15 mL) was stirred at room temperature for 7 h. The reaction mixture was poured into $Et_2O$ (20 mL) and water (20 mL). The layers were separated, and the aqueous layer was extracted with $Et_2O$ (3×20 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography (EtOAc) afforded acetamide **10a** (0.43 g, 98%) as a colorless oil: $[\alpha]_D$=−13.6° (*c* 0.25, $CHCl_3$); IR (film) 3283, 3063, 2105, 1663, 1503 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.60 (s, 1H), 7.05 (s, 1H), 6.52 (s, 1H), 6.22 (br s, 1H), 5.33–5.27 (m, 1H), 3.94 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.33 (s, 1H), 2.84–2.68 (m, 2H), 2.34–2.23 (m, 1H), 2.19–2.11 (m, 1H), 2.05 (s, 3H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 169.5, 163.8, 155.6, 154.1, 140.2, 140.0, 138.8, 126.9, 108.6, 108.1, 83.5, 78.2, 61.2, 61.0, 56.0, 47.3, 34.6, 30.4, 23.2; HRMS ($M^+$) calcd for $C_{19}H_{22}N_2O_5$ 358.1529, found 358.1541.

**(*S*)-*N*-7-Acetylamino-(12,13,14-trimethoxy-5-oxatricyclo-[8.4.0.0$^{2,6}$]tetradeca-1(10),2(6),3,11,13-pentaene (9a).** A solution of **10a** (75 mg, 0.21 mmol) in *o*-dichlorobenzene (5 mL) was degassed with nitrogen for 2 h. The mixture was heated at reflux under an atmosphere of nitrogen for 66 h and then cooled to room temperature. The mixture was concentrated in vacuo and purified by chromatography (ethyl acetate) to afford 41 mg (60%) of furan **9a** as a white solid: mp 197–198°C; $[\alpha]_D$=−14.7° (*c* 1.20, $CHCl_3$); IR (film) 3299, 3133, 1632 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.40 (d, $J$=1.9 Hz, 1H), 6.94 (d, $J$=1.9 Hz, 1H), 6.52 (s, 1H), 5.84 (d, $J$=7.7 Hz, 1H), 5.42 (dd, $J$=15.0, 7.7 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.80 (s, 3H), 2.71–2.59 (m, 2H), 2.37–2.28 (m, 1H), 2.01 (s, 3H), 1.96–1.86 (m, 1H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 169.2, 152.1, 151.8, 149.4, 141.3, 141.0, 138.0, 118.3, 116.9, 112.8, 108.4, 60.9, 60.7, 55.9, 48.6, 33.0, 31.5, 23.4; HRMS ($M^+$) calcd for $C_{18}H_{21}NO_5$ 331.1420, found 331.1431.

**(2*S*)-Methyl-[2-*tert*-butoxycarbonylamino-4-oxo-4-(3,4,5-trimethoxyphenyl)]butanoate (18).** A solution of *N*-BOC-L-iodoalanine (0.49 g, 1.49 mmol) in benzene (6 mL) and DMA (0.4 mL) was added to a flask charged with zinc-copper couple (0.180 g) and purged with nitrogen. The resulting mixture was sonicated for 3 h at room temperature to give the organozinc reagent **17**. Bis(triphenylphosphine)-palladium dichloride (63 mg, 0.09 mmol) was added, followed by 3,4,5-trimethoxybenzoyl chloride (0.35 g, 1.49 mmol) and the mixture was sonicated under an atmosphere of nitrogen for 2 h. Ethyl acetate (100 mL) was added

and the mixture was filtered into a separatory funnel. The filtrate was washed with 0.1N HCl (50 mL), water (3×40 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography (2:1 hexane–EtOAc) afforded **18** (184 mg, 31%) as a colorless oil: $[\alpha]_D$=46.3° (*c* 0.54, $CHCl_3$); IR (film) 3371, 1748, 1716, 1586, 1505 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.19 (s, 2H), 5.61 (d, *J*=8.4 Hz, 1H), 4.67 (dt, *J*=8.4, 4.0 Hz, 1H), 3.89 (s, 9H), 3.73 (s, 3H), 3.66 (d, *J*=4.0 Hz, 1H), 3.53 (d, *J*=4.0 Hz, 1H), 1.42 (s, 9H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 196.5, 171.9, 155.5, 153.1, 143.1, 131.2, 105.6, 80.0, 60.9, 56.2, 52.6, 49.6, 40.8, 28.3; HRMS ($M^+$) calcd for $C_{19}H_{27}NO_8$ 397.1737, found 397.1746.

**(2*S*)-Methyl-[2-*tert*-butoxycarbonylamino-4-(3,4,5-trimethoxyphenyl)]butanoate (19).** Palladium (5%) on charcoal (30 mg) was added to a solution of **18** (0.100 g, 0.25 mmol) in ethanol (1 mL) and water (0.2 mL). The resulting mixture was agitated under a hydrogen atmosphere at 60 psi for 22 h. The reaction mixture was filtered through a Celite pad and concentrated in vacuo. Purification by column chromatography (2:1 hexane–EtOAc) afforded **19** (89 mg, 91%) as a colorless oil: $[\alpha]_D$=30.8° (*c* 0.13, $CHCl_3$); IR (film) 3361, 1745, 1713, 1590, 1508 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 6.39 (s, 2H), 5.04 (br d, *J*=7.6 Hz, 1H), 4.37 (br s, 1H), 3.85 (s, 6H), 3.82 (s, 3H), 3.73 (s, 3H), 2.62 (t, *J*=7.9 Hz, 2H), 2.18–2.08 (m, 1H), 1.97–1.87 (m, 1H), 1.45 (s, 9H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 173.2, 155.4, 153.2, 136.5, 136.4, 105.4, 80.0, 60.8, 56.1, 53.1, 52.3, 34.4, 32.0, 28.3; HRMS ($M^+$) calcd for $C_{19}H_{29}NO_7$ 383.1944, found 383.1923.

**(2*S*)-Methyl-[2-*tert*-butoxycarbonylamino-4-(2-iodo-3,4,5-trimethoxyphenyl)]butanoate (20).** To a stirred suspension of **19** (570 mg, 1.49 mmol), sodium bicarbonate (0.25 g, 3.0 mmol), and silver trifluroacetate (0.33 g, 1.5 mmol) in $CHCl_3$ (25 mL) was added dropwise a solution of iodine (0.38 g, 1.49 mmol) in chloroform (25 mL) over a period of 1 h at 0°C. After stirring for an additional 1 h, the mixture was filtered and the precipitate was washed thoroughly with chloroform (30 mL). The solvent was removed under vacuum, and purification by column chromatography (4:1 hexane–EtOAc) afforded iodide **20** (706 mg, 93%) as a colorless oil: $[\alpha]_D$=19.4° (*c* 0.52, $CHCl_3$); $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 6.65 (s, 1H), 5.11 (br d, *J*=8.0 Hz, 1H), 4.38 (br d, *J*=4.1 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.76 (s, 3H), 2.78 (t, *J*=8.0 Hz, 2H), 2.13–2.04 (m, 1H), 1.94–1.84 (m, 1H), 1.46 (s, 9H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 172.9, 155.4, 153.6, 153.1, 140.4, 138.9, 109.0, 87.8, 79.9, 60.9, 60.7, 56.1, 52.9, 52.3, 36.8, 33.0, 28.3; HRMS ($M^+$) calcd for $C_{19}H_{28}INO_7$ 509.0911, found 509.0902.

**(2*S*)-Methyl-[2-acetamido-4-(2-iodo-3,4,5-trimethoxyphenyl)]butanoate (21).** Trifluoroacetic acid (1.22 g, 10.7 mmol) was added to a solution of **20** (544 mg, 1.07 mmol) in ether (20 mL). The solution was stirred for 3 h at room temperature and concentrated under reduced pressure. The residue was dissolved in ether (10 mL), followed by sequential addition of 4-(dimethylamino)pyridine (0.13 g, 1.07 mmol), triethylamine (3 mL), and acetic anhydride (2 mL). The reaction mixture was stirred for 10 h, concentrated under reduced pressure, and purified by chromatography (ethyl acetate) to afford **21** (454 mg, 94%) as a colorless oil: $[\alpha]_D$=34.2° (*c* 1.01, $CHCl_3$); IR (film) 3402, 1742, 1651, 1561 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 6.65 (s, 1H), 6.12 (br d, *J*=7.9 Hz, 1H), 4.70 (dt, *J*=7.9, 5.2 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.76 (s, 3H), 2.75 (t, *J*=8.1 Hz, 2H), 2.17–2.05 (m, 1H), 2.06 (s, 3H), 2.01–1.88 (m, 1H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 172.7, 169.8, 153.7, 153.1, 140.5, 138.8, 108.9, 87.8, 60.9, 60.7, 56.2, 52.5, 51.7, 36.8, 33.0, 23.2; HRMS ($M^+$) calcd for $C_{16}H_{22}INO_6$ 451.0492, found 451.0475.

**(2*S*)-Methyl-[2-acetamido-4-(2-trimethylsilylethynyl-3,4,5-trimethoxy)phenyl]butanoate (22).** To a mixture of trimethylsilylacetylene (0.36 g, 3.66 mmol), **21** (328 mg, 0.73 mmol), and diethylamine (2 mL) in DMSO (8 mL) were added bis[triphenylphosphine]palladium dichloride (31 mg, 0.04 mmol) and copper(I) iodide (17 mg, 0.09 mmol). After the reaction mixture had been stirred at 90°C for 15 h in a sealed tube, it was cooled to room temperature, poured into water (60 mL), and extracted with $CH_2Cl_2$ (3×40 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (1:1 hexane–EtOAc) afforded **22** (0.185 g, 60%) as a colorless oil: $[\alpha]_D$=21.1° (*c* 1.05, $CHCl_3$); IR (film) 3422, 2149, 1746, 1654, 1493 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 6.50 (s, 1H), 5.99 (d, *J*=8.2 Hz, 1H), 4.65 (dt, *J*=8.2, 5.0 Hz, 1H), 3.93 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.71 (s, 3H), 2.81–2.69 (m, 2H), 2.24–2.15 (m, 1H), 2.05–1.91 (m, 1H), 2.02 (s, 3H), 0.27 (s, 9H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 172.9, 169.8, 155.4, 153.8, 140.3, 139.6, 109.8, 108.1, 101.3, 99.4, 61.0, 56.0, 52.3, 51.9, 32.8, 30.8, 23.2, 0.0; HRMS ($M^+$) calcd for $C_{21}H_{31}NO_6Si$ 421.1921, found 421.1942.

**(2*S*)-Methyl-[2-acetamido-4-(2-ethynyl-3,4,5-trimethoxy)phenyl]butanoate (23).** Potassium carbonate (0.2 g, 1.4 mmol) was added to a solution of **22** (121 mg, 0.29 mmol) in MeOH (5 mL). The reaction mixture was stirred at room temperature for 11 h and poured into $CH_2Cl_2$ (20 mL) and water (20 mL). The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2×20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (EtOAc) afforded **23** (91 mg, 91%) as a colorless oil: $[\alpha]_D$=14.9° (*c* 0.7, $CHCl_3$); IR (film) 3366, 3280, 2100, 1754, 1668, 1551, 1502 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 6.48 (s, 1H), 6.32 (br d, *J*=7.9 Hz, 1H), 4.61 (dt, *J*=7.9, 5.3 Hz, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 3.67 (s, 3H), 3.36 (s, 1H), 2.79–2.64 (m, 2H), 2.18–2.08 (m, 1H), 2.02–1.90 (m, 1H), 1.99 (s, 3H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 172.8, 169.8, 155.6, 154.1, 140.3, 139.9, 108.6, 108.1, 83.5, 78.2, 61.2, 61.0, 56.0, 52.4, 51.9, 33.0, 30.4, 23.2; HRMS ($M^+$) calcd for $C_{18}H_{23}NO_6$ 349.1525, found 349.1523.

**(*S*)-*N*-Acetyl-3-(2-ethynyl-3,4,5-trimethoxyphenyl)-1-(5-oxazolyl)propylamine (10b).** A solution of **23** (100 mg, 0.29 mmol) in $CH_2Cl_2$ (4 mL) was treated at −78°C with DIBAL (0.75 mL of a 1.0 M solution in hexane). After the reaction mixture had been stirred for an additional 1 h, it was quenched by slow addition of MeOH (2 mL), followed by water (0.4 mL). The resulting mixture was allowed to warm to room temperature and diluted with ether

(30 mL), followed by $MgSO_4$ (7 g). The suspension was then stirred vigorously for 30 min and filtered through a pad of Celite. The filtercake was rinsed with ether (30 mL), and the combined filtrates were concentrated to give the corresponding aldehyde (91 mg, 100%). To a solution of the crude aldehyde in MeOH (3 mL) were added TosMIC (56 mg, 0.29 mmol) and potassium carbonate (40 mg, 0.29 mmol). The reaction mixture was heated at reflux for 1 h. After potassium hydroxide (0.23 g, 4.1 mmol) in MeOH (4 mL) had been added, the resulting mixture was stirred at reflux for 3 h, cooled to room temperature, and poured into EtOAc (30 mL) and water (30 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2×30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (EtOAc) afforded oxazole **10b** (66 mg, 64%) as a colorless oil: $[\alpha]_D=-14.0°$ (*c* 0.5, $CHCl_3$); IR (film) 3275, 2100, 1660, 1500 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.81 (s, 1H), 6.98 (s, 1H), 6.51 (s, 1H), 5.67 (br d, *J*=8.9 Hz, 1H), 5.27 (dt, *J*=8.9, 5.7 Hz, 1H), 3.96 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 3.37 (s, 1H), 2.88–2.79 (m, 1H), 2.76–2.68 (m, 1H), 2.25–2.09 (m, 2H), 2.02 (s, 3H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 169.4, 155.6, 154.1, 151.7, 150.5, 140.3, 139.9, 123.0, 108.5, 108.2, 83.6, 78.2, 61.2, 61.0, 56.0, 44.9, 34.0, 31.0, 23.2; HRMS ($M^+$) calcd for $C_{19}H_{22}N_2O_5$ 358.1529, found 358.1511

**Furan 9a.** A solution of oxazole **10b** (100 mg, 0.28 mmol) in *o*-dichlobenzene (6 mL) was degassed with nitrogen for 2 h. The mixture was heated at reflux under an atmosphere of nitrogen for 40 h and then cooled to room temperature. The mixture was concentrated in vacuo and purified by chromatography (ethyl acetate) to afford 65 mg (70%) of **9a** as a white solid: $[\alpha]_D=-15.9°$ (*c* 3.40, $CHCl_3$), which exhibited the spectroscopic data identical to that of the furan obtained from **10a**.

**(*S*)-7-*tert*-Butoxycarbonylamino-(12,13,14-trimethoxy-5-oxatricyclo[8.4.0.0$^{2,6}$]tetradeca-1(10),2(6),3,11,13-pentaene (9b).** To a solution of **9a** (182 mg, 0.55 mmol) in methylene chloride (15 mL) were added triethylamine (0.1 mL, 0.8 mmol) di-*tert*-butyl-dicarbonate (0.36 g, 1.7 mmol) and 4-(dimethylamino)pyridine (0.1 g, 0.8 mmol). The solution was stirred for 10 h at 35°C under an atmosphere of nitrogen. After the solvent had been removed under reduced pressure, the residue was purified by chromatography (2:1 hexane:ethyl acetate) to afford 0.235 g (99%) of the desired *N*-*tert*-butoxycarbonyl acetamide: $[\alpha]_D=-5.0°$ (*c* 1.20, $CHCl_3$); IR (film) 1743, 1695, 1604, 1501 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.32 (d, *J*=1.8 Hz, 1H), 6.89 (d, *J*=1.8 Hz, 1H), 6.49 (s, 1H), 6.08 (dd, *J*=10.7, 8.2 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 2.81–2.69 (m, 2H), 2.48 (s, 3H), 2.29–2.12 (m, 2H), 1.23 (s, 9H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 172.6, 152.9, 151.8, 151.6, 149.1, 140.9, 139.9, 137.1, 117.8, 117.3, 112.8, 108.4, 83.0, 60.7, 60.6, 55.9, 53.5, 32.7, 29.6, 27.5, 26.5; HRMS ($M^+$) calcd for $C_{23}H_{29}NO_7$ 431.1944, found 431.1948.

To a solution of *N*-*tert*-butoxycarbonyl acetamide in tetrahydrofuran (6 mL) was added 3.3 mL of a 1.0N solution of lithium hydroxide. The mixture was stirred for 12 h. After most of tetrahydrofuran had been removed in vacuo, the aqueous residue was acidified by addition of 10% acetic acid and extracted with ether. The organic extract was dried over $MgSO_4$, concentrated in vacuo, and purified by chromatography (1:4 hexane:ethyl acetate) to give 210 mg (99%) of **9b** as a white solid: mp 98–99°C; $[\alpha]_D=-17.5°$ (*c* 1.17, $CHCl_3$); IR (film) 3347, 1710, 1600 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.41 (d, *J*=1.8 Hz, 1H), 6.93 (d, *J*=1.8 Hz, 1H), 6.51 (s, 1H), 5.15–5.04 (m, 1H), 4.92 (br s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.77 (s, 3H), 2.70–2.58 (m, 2H), 2.31–2.23 (m, 1H), 2.00–1.99 (m, 1H), 1.47 (s, 9H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 155.2, 152.1, 151.7, 149.9, 141.2, 141.0, 138.0, 117.9, 117.1, 112.6, 108.4, 79.6, 61.0, 60.7, 55.9, 49.7, 33.5, 31.4, 28.4; HRMS ($M^+$) calcd for $C_{21}H_{27}NO_6$ 389.1838, found 389.1827.

**(1*R*,2*S*,13*R*,14*S*)-2-*tert*-Butoxycarbonylamino-7,8,9,14-tetramethoxy-17-oxatetracyclo[11.3.1.0$^{1,11}$.0$^{5,10}$]heptadeca-5(10),6,8,11(12)-tetraen-15-one (7).** A solution of **9b** (28 mg, 0.07 mmol) and **24** (17 mg, 0.09 mmol) in nitroethane (3 mL) was cooled to −78°C. Trimethylsilyl triflate (0.04 mL, 0.22 mmol) was added dropwise during 5 min. After 1 h, the reaction temperature was raised to −60°C and stirred for an additional 12 h. Saturated aqueous $NaHCO_3$ (10 mL) was added, and the product was extracted with methylene chloride (10 mL). The organic extract was dried over $MgSO_4$, concentrated, and purified by chromatography (2:1 hexane:ethyl acetate) to provide 14 mg of recovered starting material **9b** and 8 mg (45% based on the consumed **9b**) of **7** as a white solid: mp 168–170°C; $[\alpha]_D=-40.3°$ (*c* 0.4, $CHCl_3$); IR (film) 3357, 1720, 1600 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 6.43 (s, 1H), 6.42 (d *J*=1.6 Hz, 1H), 5.14 (dd, *J*=4.9, 1.6 Hz, 1H), 4.45–4.35 (br s, 1H), 4.25–4.15 (br s, 1H), 3.95 (d, *J*=4.9 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.72 (s, 3H), 3.65 (s, 3H), 2.99–2.92 (m, 1H), 2.85–2.77 (m, 1H), 2.59 (d, *J*=15.7 Hz, 1H), 2.35 (d, *J*=15.7 Hz, 1H), 2.35–2.23 (m, 1H), 1.76–1.65 (m, 1H), 1.44 (s. 9H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 204.5, 155.5, 153.3, 152.7, 140.9, 140.1, 136.0, 131.5, 117.5, 108.2, 90.2, 84.8, 78.2, 61.1, 60.6, 59.8, 55.9, 55.6, 45.2, 32.4, 31.9, 29.7, 28.4, 27.4; HRMS ($M^+$) calcd for $C_{25}H_{33}NO_8$ 475.2206, found 475.2228.

**(1*S*,2*S*,13*S*,16*R*)-2-Acetamido-7,8,9,16-tetramethoxy-17-oxatetracyclo[11.3.1.0$^{1,11}$.0$^{5,10}$]heptadeca-5(10),6,8,11(12)-tetraen-15-one (25).** A solution of **9a** (20 mg, 0.06 mmol) and **24** (12 mg, 0.12 mmol) in nitroethane (2 mL) was cooled to −78°C. Trimethylsilyl triflate (0.37 mL, 0.17 mmol) was added dropwise during 5 min. After 1 h, the reaction temperature was raised to −60°C and stirred for an additional 12 h. Saturated aqueous $NaHCO_3$ (10 mL) was added, and the product was extracted with methylene chloride (10 mL). The organic extract was dried over $MgSO_4$, concentrated, and purified by chromatography (2:1 hexane:ethyl acetate) to provide 8 mg of recovered starting material **9a** and 8 mg (60% based on the consumed **9a**) of 25: IR (film) 3331, 1766, 1666 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 6.41 (s, 1H), 6.18 (d, *J*=1.8 Hz, 1H), 5.92 (br d, *J*=9.4 Hz, 1H), 5.08 (br d, *J*=5.0 Hz, 1H), 4.55 (dt, *J*=9.4, 2.4 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.72 (s, 3H), 3.70 (s, 1H), 3.41 (s, 3H), 2.99 (t, *J*=7.1 Hz, 2H), 2.85 (dd, *J*=15.8, 5.0 Hz, 1H), 2.54 (d, *J*=15.8 Hz, 1H), 2.24–2.13 (m, 1H), 2.04 (s, 3H), 1.83–1.75

(m, 1H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 205.4, 170.5, 161.0, 154.6, 152.6, 136.4, 133.2, 132.7, 116.9, 109.2, 91.4, 87.2, 61.2, 61.0, 60.6, 56.0, 55.8, 45.7, 34.5, 30.9, 27.3, 23.5; HRMS ($M^+$) calcd for $C_{22}H_{27}NO_7$ 417.1788, found 417.1799.

**(*S*)-7-*tert*-Butoxycarbonylamino-6,7-dihydro-1,2,3,10-tetramethoxybenzo[*a*]heptalene-9(5*H*)-one (26).** Trimethylsilyl triflate (0.08 mL, 0.45 mmol) was added dropwise at 0°C to a solution of **7** (0.014 g, 0.04 mmol) and triethylamine (0.17 mL, 1.2 mmol) in methylene chloride (2 mL). After 2 h, saturated aqueous $NaHCO_3$ (5 mL) was added, and the product was extracted with methylene chloride (10 mL). The organic extract was dried over $MgSO_4$, concentrated, and purified by chromatography (ethyl acetate) to afford 9 mg (62%) of **26** as a white solid: mp 230–232°C; $[\alpha]_D$=−113.4° (*c* 0.51, $CHCl_3$); IR (film) 3432, 1710, 1625, 1592 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.48 (s, 1H), 7.24 (d, *J*=10.8 Hz, 1H), 6.79 (d, *J*=10.8 Hz, 1H), 6.52 (s, 1H), 4.98 (d, *J*=6.8 Hz, 1H), 4.45–4.35 (m, 1H), 3.98 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H), 3.64 (s, 3H), 2.52–2.47 (m, 1H), 2.38 (dt, *J*=6.8, 12.8 Hz, 1H), 2.31–2.18 (m, 1H), 1.75–1.62 (m, 1H), 1.35 (s, 9H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 179.5, 163.9, 154.3, 153.4, 151.1, 141.6, 136.0, 134.9, 134.2, 131.1, 125.6, 112.0, 107.2, 79.8, 61.4, 61.3, 56.2, 56.0, 53.0, 37.6, 29.9, 29.6, 28.3; HRMS ($M^+$) calcd for $C_{25}H_{31}NO_7$ 457.2101, found 457.2099.

**Colchicine (1).** A solution of **26** (5 mg, 0.01 mmol) in ether (1 mL) was treated with 3 mL of 1.0 M solution of hydrogen chloride in ether. The solution was stirred for 1 h at room temperature and concentrated under reduced pressure. The residue was dissolved in ether (3 mL), and 4-(dimethylamino)pyridine (3 mg, 0.02 mmol), triethylamine (0.01 mL, 0.07 mmol) and acetic anhydride (0.01 mL) were added. The reaction mixture was stirred for 10 h at 25°C, concentrated under reduced pressure, and purified by chromatography (ethyl acetate) to afford 4 mg (98%) of colchicine (**1**) as a white solid: mp 153–155°C; $[\alpha]_D$=−143.5° (*c* 0.58, $CHCl_3$); IR (film) 3279, 3055, 1667, 1620, 1598 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.79 (d, *J*=6.4 Hz, 1H), 7.59 (s, 1H), 7.34 (d, *J*=10.8 Hz, 1H), 6.88 (d, *J*=10.8 Hz, 1H), 6.53 (s, 1H), 4.69–4.62 (dt, *J*=6.4, 12.2 Hz, 1H), 4.01 (s, 3H), 3.94 (s, 3H), 3.90 (s, 3H), 3.65 (s, 3H), 2.55–2.47 (m, 1H), 2.44–2.27 (m, 2H), 1.97 (s, 3H), 1.91–1.80 (m, 1H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 179.5, 170.0, 164.0, 153.5, 152.4, 151.2, 141.7, 136.9, 135.6, 134.2, 130.5, 125.6, 112.8, 107.3, 61.6, 61.4, 56.4, 56.1, 52.7, 36.5, 29.9, 22.8; HRMS ($M^+$) calcd for $C_{22}H_{25}NO_6$ 399.1682, found 399.1657.

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