DOI: 10.1002/ejoc.200800595

Synthesis of New Allocolchicinoids with Seven- and Eight-Membered B-Rings by Enyne Ring-Closing Metathesis

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Keywords: Allocolchicines / Enyne / Ring-closing metathesis / Cycloheptenes / Cyclooctenes / Diels–Alder reactions

Total syntheses of allocolchicines **4** and **5**, with the ester functionality in the C-ring at the C10 or C11 positions, is reported. An asymmetric synthesis of (7*S*)-allocolchicine **5** is also described. The main features included the elaboration of a common intermediate, the AB bicyclic ring system, in which the construction of the seven-membered ring was achieved by an enyne ring-closing metathesis (RCM) reaction. A subsequent Diels–Alder/aromatization sequence afforded the set of functionalized ring-C allocolchicinoids with high regioselectivity. This strategy was also applied for the synthesis of allocolchicine **6**, containing an eight-membered B-ring.

Introduction

Colchicine (**1**), present as the major alkaloid in *Colchicum autumnale*, is an old drug used in medicine in acute gout attacks and in familial Mediterranean fever. It has long been known for its remarkable antimitotic activity, the result of its specific binding to tubulin, preventing microtubule assembly, spindle formation, and consequently cell division.[1,2] Colchicine has also been studied as an anticancer agent, but therapeutic effects are only observed at toxic or nearly toxic doses. A significant development in cancer chemotherapy was the discovery that allocolchicinoids, possessing a benzene ring in place of the tropolone ring, also arrest mitosis by inhibiting tubulin polymerization. Natural allocolchicine (**2**) binds to tubulin more strongly than colchicine itself.[3] Recently, colchicine-type antimicrotubule agents found a second wind with the discovery that *N*-acetylcolchinol (**3**), in the form of its water-soluble phosphate, selectively induces tumor vascular damage and tumor necrosis at well-tolerated doses; it is currently undergoing clinical trials.[4]

For a long time allocolchicinoids were obtained by transformation of colchicine itself, thus limiting the range of structural variations. Recently, total syntheses of **2** and **3** have been reported, and a number of syntheses of various allocolchicinoids have also been described.[5] Whereas most approaches involve a strategy based on the construction of the seven-membered ring by an intramolecular biaryl coupling reaction (AC → ABC approach), a different route was developed by Wulff and co-workers, distinguished by the construction of the aromatic C-ring through a Diels–Alder reaction of a suitably substituted diene containing the seven-membered ring (AB → ABC approach).[5a] In all these approaches, the allocolchicinoids described bear functionalities at the C9 position in the C-ring.[6]

In the course of our study of the application of metathesis reactions of enynes to the synthesis of polycyclic compounds containing seven-membered rings,[7] we recently described the synthesis of the new allocolchicines **4** and **5** (Figure 1),[8] analogues of **2** containing the ester group at positions C10 and C11, respectively.[7c] Here we report a full account of this work and also describe an asymmetric synthesis of (7*S*)-allocolchicine **5**, together with the synthesis of a new allocolchicinoid **6**, an analogue of **5** in which the seven-membered B-ring is replaced by an eight-membered ring.

Our route was based on a conceptually similar approach to Wulff's one. The construction of the allocolchicine tricyclic core was planned to be through a Diels–Alder reaction with a suitably substituted diene containing either a seven- or an eight-membered ring fused to the aromatic A-ring (AB → ABC approach). As shown in the retrosynthetic analysis (Scheme 1), target compounds **4**, **5**, and **6** were to be obtained by direct reductive amination of ketones **7**, **8**, and **9**, respectively. These ketones could be prepared by a Diels–Alder/aromatization sequence from intermediate dienes **10** (*n* = 1 or 2), which can be traced back to **11** (R = TBS). Our initial plan involved the preparation of **11** by ring-closing metathesis (RCM) of enyne **12**.[9] This precursor was to be obtained from the cheap and commercially available acid **13**.

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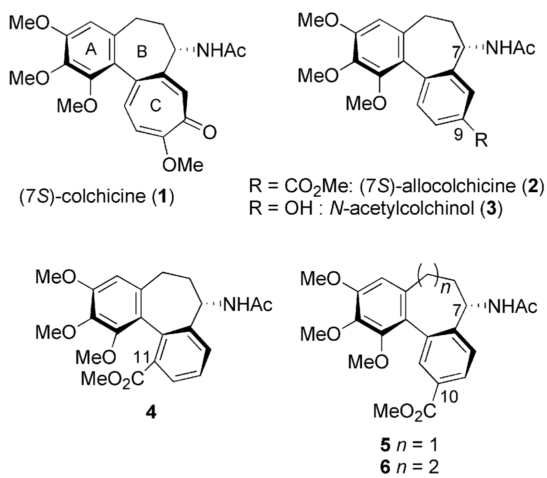
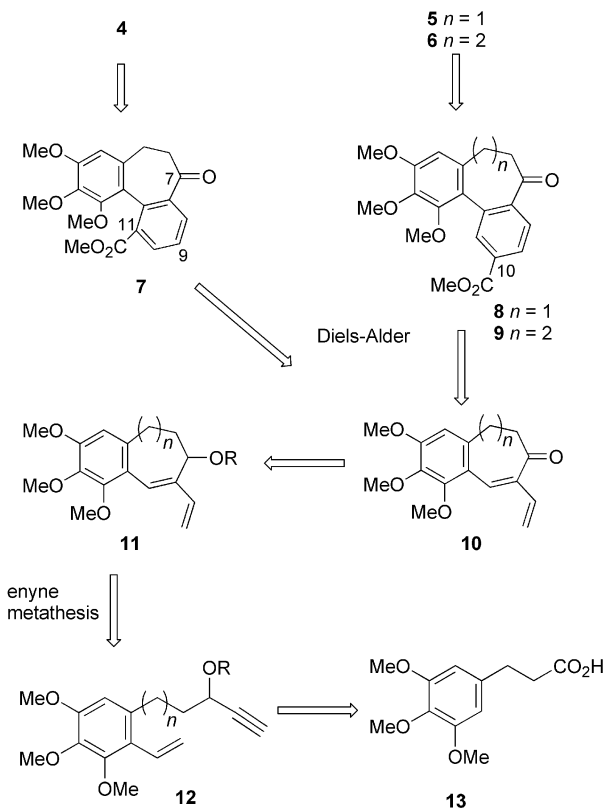


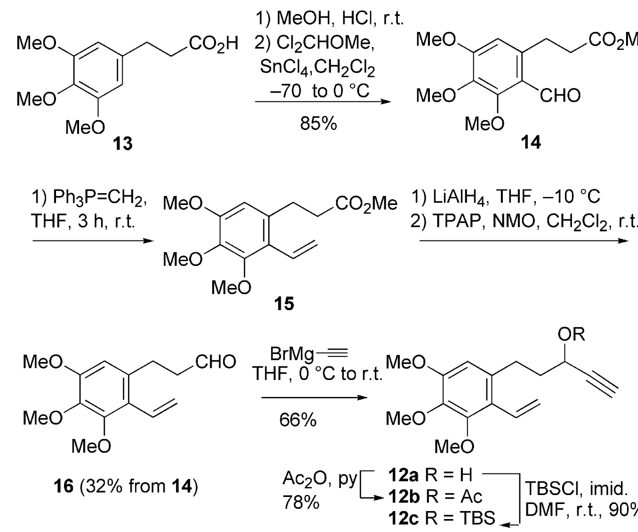
Figure 1. Colchicine and allocolchicines.



Scheme 1. Initial retrosynthesis of allocolchicines.

Results and Discussion

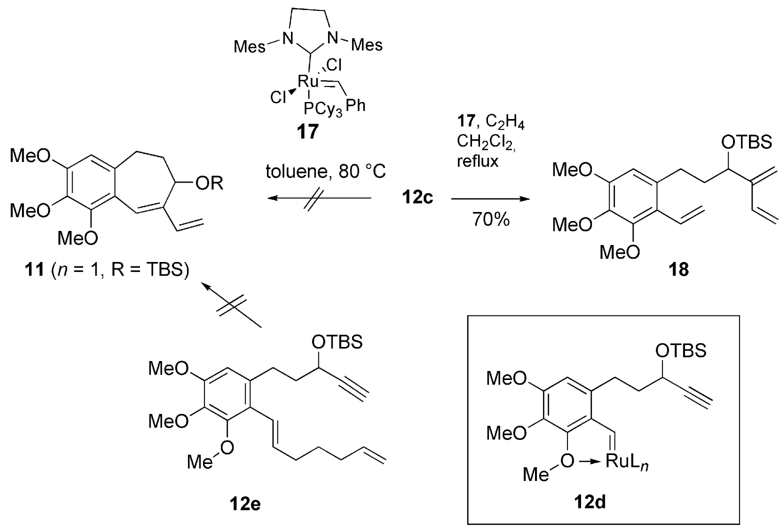
According to this strategy, the synthesis commenced with the conversion of the acid functionality of **13** into the methyl ester and subsequent formylation with dichloromethyl methyl ether in the presence of $SnCl_4$ to afford aldehyde **14** (Scheme 2).[10] A Wittig reaction converted this aldehyde into ester **15**. Reduction of **15** with $LiAlH_4$ and subsequent oxidation of the resulting primary alcohol led to aldehyde **16**. Treatment of **16** with ethynylmagnesium bromide afforded propargylic alcohol **12a**, which was converted either into acetate **12b** or into silyl ether **12c**. These enynes were then subjected to RCM conditions. Unfortunately, when these compounds were treated with the second-generation Grubbs catalyst (**17**),[11] either in CH_2Cl_2 at reflux or in toluene at 80 °C, no ring-closing product such as **11** was isolated. When this reaction was carried out on diene **12c** under ethylene gas[12] in CH_2Cl_2 at reflux for 22 h, however, compound **18** was obtained as the sole product in 70% yield (Scheme 3). We were therefore intrigued by the potential application of Hoye's relay RCM strategy[13] for delivering the catalyst onto the alkene. To this end, dienyne **12e** was prepared[14] and subjected to various sets of RCM conditions in the presence of catalyst **17**. In all cases none of the desired product was formed. These data suggested that, in the absence of ethylene, the terminal alkene in **12c** reacts more readily with the (alkylidene)Ru unit to afford the chelated complex **12d**, which sequesters the active Ru system, inhibiting cyclization to **11**.[15]



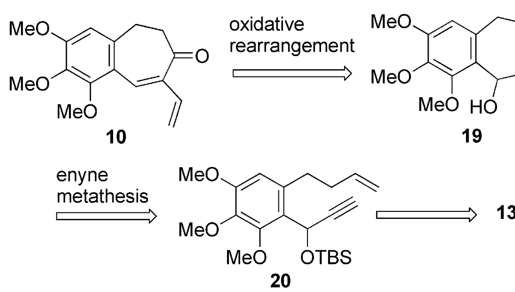
Scheme 2. Preparation of enyne **12** ($n = 1$).

In view of the above result, we turned to another strategy starting from enyne **20**, in which the formation of a seven-membered ring by RCM would be followed by an oxidative rearrangement of allylic alcohol **19** to furnish ketone **10** (Scheme 4). It was already known that, contrary to **12c**, enyne **20** would easily undergo the ring-closing metathesis reaction.[16]

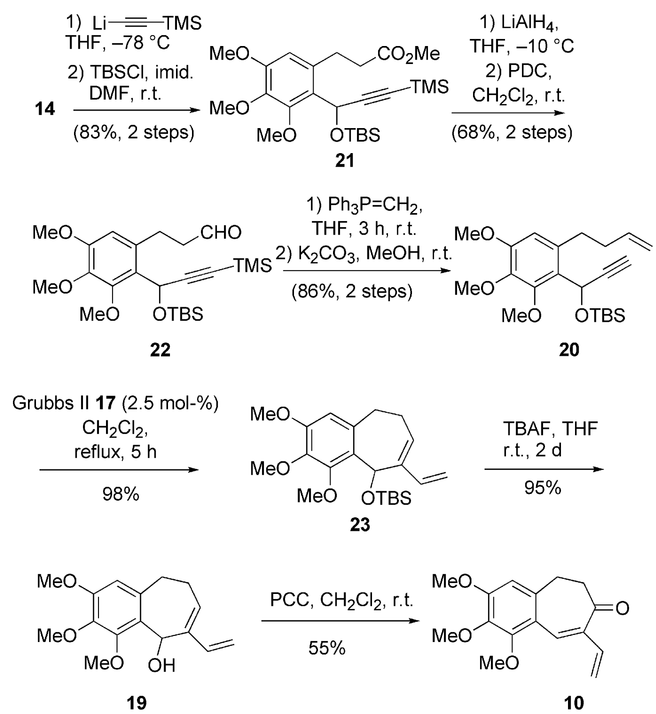
The RCM precursor **20** was prepared from aldehyde **14** as indicated in Scheme 5. Compound **14** was alkynylated with lithiated trimethylsilylacetylene, and the resulting propargylic alcohol was converted into its *tert*-butyldimethylsilyl-protected derivative **21** under standard conditions. To elaborate the "upper" carbon chain, ester **21** was reduced with $LiAlH_4$, and the resulting primary alcohol was treated with PDC to furnish aldehyde **22**. Conversion of **22** into enyne **20** was accomplished by a Wittig reaction followed by selective desilylation with K_2CO_3 in MeOH. Treatment of **20** with the second-generation Grubbs catalyst (2.5%) in dichloromethane at reflux for 5 h smoothly afforded diene **23** in 98% yield. Complete deprotection of the secondary alcohol was achieved by stirring **23** with tetrabutylammo-



Scheme 3. Attempted RCM of enyne **12c**.



Scheme 4. Revised approach to the bicyclic ring system.



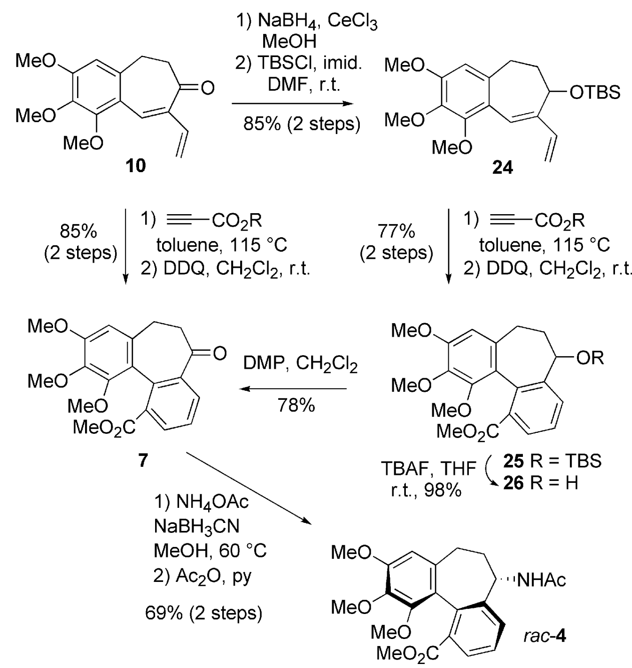
Scheme 5. Synthesis of the common intermediate **10**.

nium fluoride (TBAF, 1 M) solution in THF at room temperature for 2 d, leading to alcohol **19**.

With the bicyclic conjugated diene **19** to hand, we next turned to the construction of the aromatic ring. To place the C-ring in its correct position through a Diels–Alder reaction, rearrangement of the allylic alcohol moiety would have to be achieved at this stage. To this end, treatment of **19** under Dauben's tertiary allylic rearrangement conditions was considered.[17a] When a solution of **19** in dichloromethane was stirred with 2 equiv. of pyridinium chlorochromate (PCC) at room temperature for 1 h, dienone **10** was obtained as the sole product in 55% yield.[17b] Sequential reduction of **10** under Luche's conditions[18] and protection of the resulting alcohol as its *tert*-butyldimethylsilyl ether under standard conditions led to **24** in high yield (Scheme 6).

A Diels–Alder reaction of diene **24** was first performed with methyl propiolate. When a mixture of **24** and an excess of this dienophile was heated in toluene at 115 °C for 24 h, only one regioisomer was obtained, as indicated by NMR spectroscopic data. The regioselectivity of this cycloaddition was confirmed in the next step: DDQ aromatization of the crude cycloadduct afforded the protected allocolchicinoid **25** as only one isomer. It is likely that electronic factors prevail over steric interactions in **24** and are responsible for this total regiocontrol. Deprotection with TBAF led to alcohol **26**, which was oxidized with Dess–Martin periodinane[19] to give ketone **7** as a white solid (m.p. 147–148 °C). It is worthy of note that alcohol **26** existed as a mixture of two atropoisomers. In these compounds the barrier of the rotation about the aryl bond is so high that the individual isomers can be separated at room temperature by silica gel column chromatography.[20]

In order to shorten the synthesis, the Diels–Alder reaction with methyl propiolate was attempted directly with dienone **10**. We were pleased to observe that this reaction

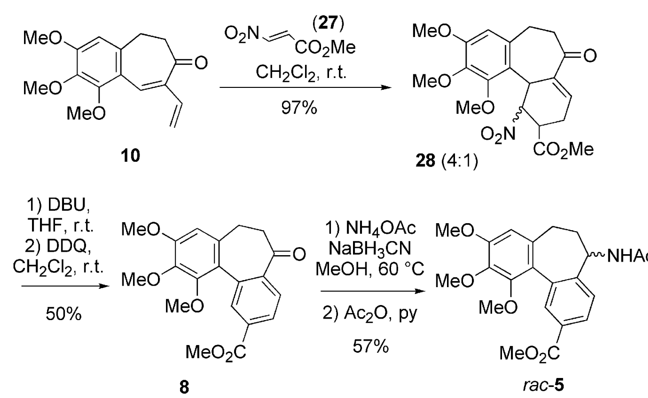


Scheme 6. Synthesis of *rac*-**4**.

occurred readily under the same conditions, affording only one regioisomer as in the case of diene **24**. Treatment of the crude cycloadduct with DDQ led to **7** in 85% overall yield (Scheme 6). In this way, the synthesis of allocolchicinoid **7** was achieved in two steps from ketone **10** instead of six for the previous sequence.

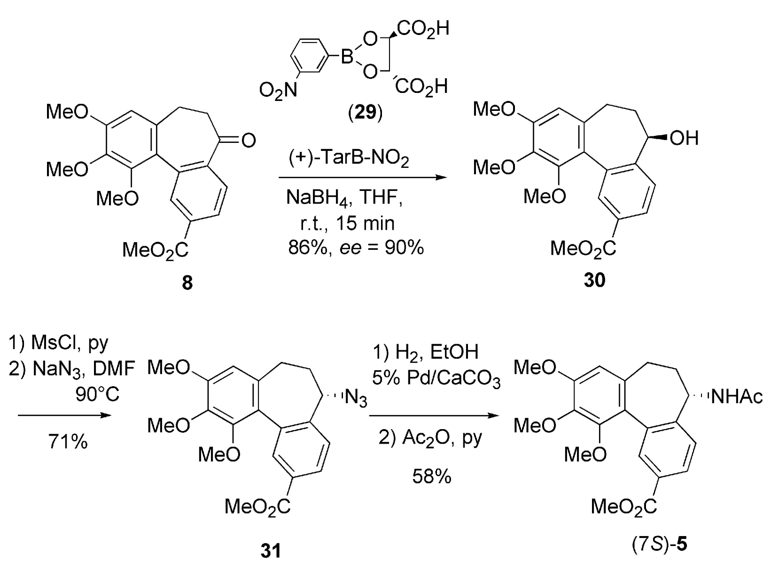
Reductive amination of ketone **7** with ammonium acetate and sodium cyanoborohydride,[21] followed by *N*-acylation of the resulting amino ester, produced *rac*-**4** (m.p. 206–209 °C) in 69% yield as a 2:1 mixture of atropoisomers as shown by ^{1}H NMR spectroscopy.

We next turned to the synthesis of allocolchicinoids with functionality at C-10. On the basis of the regioselectivity observed above, we reasoned that methyl β-nitroacrylate (**27**;[22] Scheme 7) should provide the opposite regiochemistry to that obtained with methyl propiolate in a Diels–Alder reaction with diene **10**. Indeed, **27** readily reacted with diene **10** at *room temperature*, affording cycloadduct **28** in 97% yield. NMR spectroscopy revealed that **28** was a mixture of two stereoisomers (4:1 ratio) confirming the complete regioselectivity of this reaction.[23] The elimination of nitrous acid by treatment with DBU and subsequent aromatization with DDQ furnished ketone **8** as the sole product in 50% overall yield. As in the case of ketone **7**, reductive amination of compound **6**, followed by *N*-acylation of the resulting amino ester, produced *rac*-**5** (m.p. 181–183 °C) in 57% yield as a 2:1 mixture of rotamers as shown by ^{1}H NMR spectroscopy.



Scheme 7. Synthesis of *rac*-**5**.

In order to gain some indication of their ability to function as antimitotic agents, racemic allocolchicines **4** and **5** described above were subjected to a tubulin binding assay.[24] While *rac*-**4** was inactive, allocolchicine *rac*-**5** was found to be as active as colchicine. This result prompted us to consider the enantioselective synthesis of **5**.



Scheme 8. Synthesis of (7*S*)-allocolchicine (**5**).

This synthesis was based on the introduction of the stereogenic center at C7 by asymmetric reduction of the ketone **8**. In their synthesis of the natural (–)-(7*S*)-allocolchicine (**2a**), Wulff and co-workers reported[5a] that the procedure developed by Singaram and co-workers for the enantioselective reduction of ketones with (+)-TarB-NO_2 (**29**)[25] had been found to give the best yields of the (7*R*)-alcohol.[26] When ketone **8** was treated with 2 equiv. of (+)-TarB-NO_2 and 2.1 equiv. of $NaBH_4$, alcohol (7*R*)-**30** was obtained in 86% yield and 90% *ee* (Scheme 8). Inversion of stereochemistry at C7 with concomitant introduction of a nitrogen functionality was achieved by a two-step procedure, to afford (7*S*)-**31** in 71% overall yield. The reduction of the azide **31** to the corresponding amine was achieved by heterogeneous hydrogenation in the presence of 5% Pd/$CaCO_3$/3.5% Pb, affording (–)-(7*S*)-allocolchicine (**5**) in 58% yield after acetylation. The enantiomeric purity of **5**, determined by chiral HPLC, was 94% after a single recrystallization.

Synthesis of Allocolchicinoids Containing an Eight-Membered B-Ring

The antimitotic activity of allocolchicine (**5**) made us interested in hitherto unknown allocolchicinoids containing an eight-membered B-ring. Such compounds belong to lignan derivatives possessing the dibenzocyclooctadiene skeleton and, like allocolchicinoids, they are characterized by an atropoisomeric biaryl unit.[20] A number of these products display a wide variety of biological activities. Naturally occurring steganacin (Figure 2), for example, binds to the colchicine site in tubulin and shows antitumor activity in vivo.[27] The syntheses of all dibenzocyclooctadiene lignan derivatives described to date, including aza and oxa analogues of steganacin, have involved inter- or intramolecular biaryl coupling reactions (AC → ABC approaches).[27,28] As in the cases of allocolchicines **4** and **5**, we planned the construction of the tricyclic core of the lignan derivatives by the AB → ABC approach. The AB part containing the eight-membered ring fused to the aromatic A-ring would thus have to be built by means of a ring-closing metathesis reaction of a suitably substituted enyne (Scheme 9).[29]

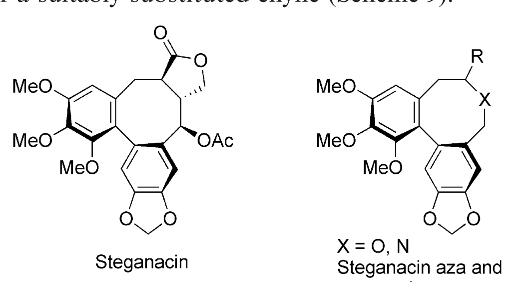
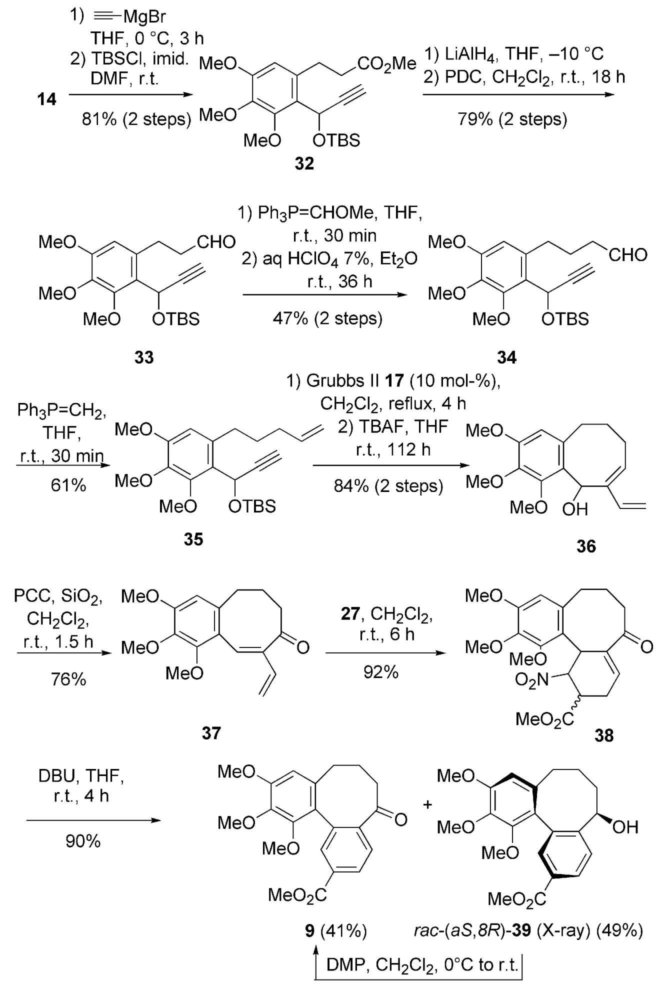


Figure 2. Dibenzocyclooctadiene lignans.

The synthesis commenced with the previously described aldehyde **14** (Scheme 9). Addition of ethynylmagnesium bromide to **14**, followed by protection of the resulting propargylic alcohol, afforded *tert*-butyldimethylsilyl ether **32** in high overall yield. To elaborate the "upper" carbon chain,



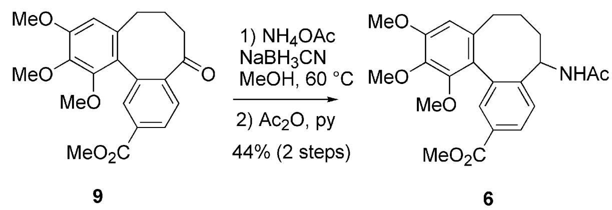
Scheme 9. Synthesis of allocolchicinoids containing an eight-membered B-ring.

ester **32** was reduced with $LiAlH_4$, and the resulting primary alcohol was treated with PDC to furnish aldehyde **33**. One-carbon homologation was achieved in a two-step sequence transforming **33** into **34** as shown in Scheme 9, and the resulting aldehyde **34** was converted into enyne **35** by a Wittig reaction.

When enyne **35** was treated with the Grubbs second-generation catalyst (10%) in dichloromethane at reflux for 4 h, the RCM reaction took place smoothly to afford, after desilylation, the bicyclic conjugated diene **36** in 84% overall yield. Obviously, this process was facilitated by the presence of the pre-existing aromatic ring bearing the alkene and alkyne moieties at adjacent positions.[30]

The introduction of the C-ring was achieved as in the case of the synthesis of allocolchicine **5**. Oxidation of alcohol **36** with pyridinium chlorochromate (PCC) at room temperature for 1.5 h afforded dienone **37** as the sole product in 76% yield. As in the case of dienone **11**, **37** readily reacted with β-nitroacrylate **27** at *room temperature* to afford cycloadduct **38** in a near quantitative yield as a mixture of diastereomers. Unexpectedly, treatment of **38** with DBU at room temperature for 4 h achieved both elimination of nitrous acid and aromatization, leading to a mixture of ketone **9** and alcohol **39** (1:1 ratio) in 90% combined yield. Oxidation of **39** with Dess–Martin periodinane reagent gave ketone **9** in 96% yield. It is worth noting that alcohol **39** was isolated as a single isomer as shown by ^{1}H NMR spectroscopy. Assignment of the relative configuration (a*S*,8*R*) of this compound was based on the X-ray crystallographic analysis.[31] For this diastereoisomer the two aryl rings are twisted out of plane with a torsion angle of about 61°.

Reductive amination of ketone **9**, followed by *N*-acylation of the resulting amino ester, produced allocochicinoid **6** (m.p. 156–158 °C) in 44% yield as a 2:1 mixture of atropoisomers as shown by ^{1}H NMR (Scheme 10).



Scheme 10. Reductive amination of ketone **39**.

Conclusions

Total syntheses of (±)-allocolchicines **4** and **5** were achieved by use of the enyne ring-closing metathesis (RCM) reaction for the construction of the seven-membered ring and a Diels–Alder/aromatization sequence for the elaboration of the aromatic C-ring. An asymmetric synthesis of (–)-(7*S*)-allocolchicine (**5**) was also accomplished. The same strategy was applied for the synthesis of allocolchicine **6**, containing an eight-membered B-ring. These new allocolchicines will be subjected to tubulin binding assay in order to gain some indication of their potential as antimitotic agents; the results will be reported in due course.

Experimental Section

Aldehyde 14: A solution of 3-(3,4,5-trimethoxyphenyl)propionic acid (**13**, 25 g, 111.6 mmol) in MeOH (265 mL) and concentrated HCl (37%, 1.75 mL) was stirred at room temperature for 24 h. The reaction mixture was neutralized with saturated sodium hydrogen carbonate solution, and MeOH was evaporated off under reduced pressure. The residue was extracted with EtOAc (3 × 30 mL), and the combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$), and concentrated under reduced pressure to furnish the crude methyl ester as a slightly yellow solid (25.8 g, 101.6 mmol, 91%). α,α-Dichloromethyl methyl ether (27.43 mL, 304.8 mmol) was added at room temperature under argon to a solution of the methyl ester (25.8 g, 101.6 mmol) in CH_2Cl_2 (254 mL). This mixture was cooled to –70 °C, and neat $SnCl_4$ (11.68 mL, 101.6 mmol) was added dropwise. The resulting yellow reaction mixture was warmed slowly to 0 °C (2 h), and water was added dropwise. The mixture was diluted with CH_2Cl_2 (500 mL) and neutralized with aqueous saturated sodium hydrogen carbonate solution and solid $NaHCO_3$. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 500 mL). The combined organic extracts were washed with brine (500 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (cyclohexane/EtOAc, 4:1) to give **14** (27 g, 95.7 mmol, 85%) as a white solid. R_f = 0.4 (cyclohexane/EtOAc, 4:1). M.p. 54–55 °C. ^{1}H NMR: δ = 10.36 (s, 1 H), 6.58 (s, 1 H), 3.97 (s, 3 H), 3.91 (s, 3 H), 3.86 (s, 3 H), 3.65 (s, 3 H), 3.22 (t, J = 7.5 Hz, 2 H), 2.61 (t, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR: δ = 190.6 (CH), 173.4 (C), 158.6 (C), 157.9 (C), 140.2 (C), 140.1 (C), 120.0 (C), 110.2 (CH), 62.3 (CH_3), 60.8 (CH_3), 56.0 (CH_3), 51.4 (CH_3), 35.0 (CH_2), 29.6 (CH_2) ppm. IR (neat): $\tilde{\nu}_{max}$ = 2946, 2850, 1735, 1678, 1590 cm^{-1}. MS (CI, NH_3): m/z (%) = 283 [M + 1]$^{+\cdot}$ (100), 300 [M + 18]$^{+\cdot}$ (5). HMRS (EI): m/z calcd. for $C_{14}H_{18}O_6$ 282.1103; found 282.1105.

Alkyne 21: *n*-Butyllithium (4.4 mL, 7.04 mmol, 1.6 M solution in hexane) was added dropwise under argon at –70 °C to a solution of ethynyltrimethylsilane (0.99 mL, 7 mmol) in dry THF (28 mL). The resulting mixture was stirred at –70 °C for 15 min, and this solution (27 mL) was added dropwise under argon at –70 °C to a solution of aldehyde **14** (1.58 g, 5.60 mmol) in dry THF (30 mL). The reaction mixture was stirred at –70 °C for 1.5 h, saturated ammonium chloride solution (20 mL) was added, and the mixture was diluted with Et_2O (100 mL). The biphasic mixture was allowed to warm to room temperature, was separated, and the aqueous phase was extracted with Et_2O (2 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give crude propargylic alcohol (2.09 g). This crude propargylic alcohol (2.09 g) was immediately dissolved in dry DMF (5 mL). Imidazole (1.156 g, 17 mmol) and *tert*-butyldimethylsilyl chloride (2.56 g, 17 mmol) were added at room temperature under argon, and the mixture was stirred for 18 h. The reaction mixture was diluted with Et_2O (100 mL), washed with HCl solution (1 N, 50 mL), H_2O (50 mL), and brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/EtOAc, 9:1) to give alkyne **21** (2.30 g 4.65 mmol, 83%) as a colorless oil. R_f = 0.6 (cyclohexane/EtOAc, 7:3). ^{1}H NMR: δ = 6.57 (s, 1 H), 6.02 (s, 1 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.68 (s, 3 H), 3.34 (t, J = 8.4 Hz, 2 H), 2.74 (t, J = 8.4 Hz, 2 H), 0.90 (s, 9 H), 0.19 (s, 3 H), 0.12 (s, 9 H), 0.09 (s, 3 H) ppm. ^{13}C NMR: δ = 173.8 (C), 152.8 (C), 150.6 (C), 139.9 (C), 136.9 (C), 125.9 (C), 109.7 (CH), 107.5 (C), 89.3 (C), 61.6 (CH_3), 60.7 (CH_3), 57.9 (CH), 55.8 (CH_3), 51.3 (CH_3), 36.1 (CH_2), 27.7 (CH_2), 25.8 (CH_3), 18.1 (C), –0.4 (CH_3), –4.7 (CH_3), –4.9 (CH_3) ppm. IR (neat): $\tilde{\nu}_{max}$ = 2954, 2856, 2169, 1739 cm^{-1}. HMRS (EI): m/z calcd. for $C_{25}H_{42}O_6Si_2$ 494.2520; found 494.2538.

Aldehyde 22: A solution of $LiAlH_4$ (336 mg, 8.84 mmol) in THF (9 mL) was added dropwise under argon to a solution of aldehyde **21** (2.30 g, 4.65 mmol) in anhydrous THF (74 mL). The reaction mixture was stirred at –10 °C for 30 min and quenched by successive addition of H_2O (336 µL), NaOH solution (15%, 336 µL), and H_2O (1020 µL). The solution was filtered, and the granular inorganic precipitate was rinsed with Et_2O (200 mL). The combined organic layers were concentrated under reduced pressure to give the crude alcohol (2.17 g), which was used in the next step without further purification. This crude alcohol (2.17 g, 4.65 mmol) was dissolved in dry CH_2Cl_2 (65 mL). PDC (5.25 g, 13.95 mmol) was added at room temperature under argon, and the mixture was stirred for 18 h. The reaction mixture was diluted with Et_2O (300 mL), filtered through Florisil®, and eluted with Et_2O. The combined organic phases were concentrated under reduced pressure, and the residue was purified by chromatography on silica gel (cyclohexane/EtOAc, 4:1) to give aldehyde **22** (1.48 g, 3.18 mmol, 68%) as a colorless oil. R_f = 0.3 (cyclohexane/EtOAc, 9:1). ^{1}H NMR: δ = 9.83 (t, J = 1.5 Hz, 1 H), 6.53 (s, 1 H), 6.03 (s, 1 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.38–3.32 (m, 2 H), 2.88–

2.83 (m, 2 H), 0.89 (s, 9 H), 0.19 (s, 3 H), 0.12 (s, 9 H), 0.09 (s, 3 H) ppm. ^{13}C NMR: δ = 202.1 (C), 152.8 (C), 150.6 (C), 139.9 (C), 136.6 (C), 125.7 (C), 109.6 (CH), 107.4 (C), 89.3 (C), 61.6 (CH_3), 60.7 (CH_3), 57.8 (CH), 55.7 (CH_3), 45.9 (CH_2), 25.7 (CH_3), 24.8 (CH_2), 18.1 (C), –0.4 (CH_3), –4.8 (CH_3), –5.0 (CH_3) ppm. IR (neat): $\tilde{\nu}_{max}$ = 2955, 2857, 2712, 2169, 1725 cm^{-1}. HMRS (EI): *m/z* calcd. for $C_{24}H_{40}O_5Si_2$ 464.2414; found 464.2427.

Enyne 20: *n*-Butyllithium (8 mL, 12.8 mmol, 1.6 M solution in hexane) was added dropwise under argon at room temperature to a solution of methyltriphenylphosphonium bromide (4.585 g, 12.85 mmol) in dry THF (30 mL). The resulting yellow-orange solution was stirred at room temperature for 45 min and cooled to 15 °C, and a solution of aldehyde **22** (1.48 g, 3.189 mmol) in dry THF (30 mL) was added dropwise under argon to the resulting ylide solution, which was maintained at 15 °C. The reaction mixture was stirred at room temperature for 30 min, and water (30 mL) was added. The biphasic mixture was separated, and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was dissolved in pentane (300 mL), filtered, and concentrated under reduced pressure to give the crude alkene (1.6 g) as a yellow oil, which was used in the next step without further purification. The crude alkene (1.6 g) was dissolved in MeOH (22 mL), and K_2CO_3 (216 mg, 1.56 mmol) was added. The reaction mixture was stirred at room temperature for 4 h, and MeOH was evaporated under reduced pressure without warming. The residue was dissolved in CH_2Cl_2 (100 mL), and the organic phase was washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/EtOAc, 95:5) to give enyne **20** (1.08 g, 2.77 mmol, 86%) as a colorless oil. R_f = 0.6 (cyclohexane/EtOAc, 9:1). ^{1}H NMR: δ = 6.59 (s, 1 H), 6.07–6.03 (m, 1 H), 6.03–5.90 (m, 1 H), 5.15–5.08 (m, 1 H), 5.04–4.99 (m, 1 H), 3.89 (s, 3 H), 3.86 (s, 6 H), 3.20–2.97 (m, 2 H), 2.50–2.41 (m, 2 H), 0.91 (s, 9 H), 0.21 (s, 3 H), 0.09 (s, 3 H) ppm. ^{13}C NMR: δ = 152.7 (C), 150.5 (C), 139.7 (C), 138.7 (CH), 137.9 (C), 125.4 (C), 114.3 (CH_2), 109.5 (CH), 85.4 (C), 72.4 (CH), 61.5 (CH_3), 60.6 (CH_3), 57.3 (CH), 55.7 (CH_3), 35.4 (CH_2), 31.6 (CH_2), 25.7 (CH_3), 18.1 (C), –4.9 (CH_3), –5.1 (CH_3) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3284, 2930, 2855, 2111 cm^{-1}. HMRS (EI): *m/z* calcd. for $C_{22}H_{34}O_4Si$ 390.2226; found 390.2224.

Metathesis of Enyne 20. Diene 23: Grubbs catalyst II (**17**, 30 mg, 2.5 mol-%) was added under nitrogen to a degassed solution of enyne **20** (552 mg, 1.415 mmol) in dry CH_2Cl_2 (30 mL). The mixture was heated at reflux for 5 h and allowed to cool to room temperature. The solvent was removed, and the residue was subjected to flash chromatography on silica gel (EtOAc/petroleum ether, 2.5:97.5) to give the diene **23** (540 mg, 1.385 mmol, 98%) as a colorless oil. R_f = 0.2 (cyclohexane/EtOAc, 95:5). ^{1}H NMR: δ = 6.50 (s, 1 H), 6.31 (dd, *J* = 17.1, 10.8 Hz, 1 H), 5.97 (s, 1 H), 5.69 (t, *J* = 4.2 Hz, 1 H), 5.39 (d, *J* = 17.1 Hz, 1 H), 4.99 (d, *J* = 10.8 Hz, 1 H), 4.06 (td, *J* = 13.5, 4.5 Hz, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.76 (s, 3 H), 2.62 (qd, *J* = 19.2, 3.3 Hz, 1 H), 2.44–2.22 (m, 2 H), 0.80 (s, 9 H), 0.09 (s, 3 H), –0.17 (s, 3 H) ppm. ^{13}C NMR: δ = 152.2 (C), 150.3 (C), 141.1 (CH), 140.0 (C), 139.2 (C), 138.0 (C), 134.7 (CH), 128.3 (C), 109.4 (CH_2), 108.9 (CH), 62.0 (CH_3), 61.7 (CH_3), 60.8 (CH), 55.9 (CH_3), 30.8 (CH_2), 30.1 (CH_2), 25.7 (CH_3), 18.0 (C), –4.8 (CH_3), –5.1 (CH_3) ppm. IR (neat): $\tilde{\nu}_{max}$ = 2928, 2855, 1637, 1598 cm^{-1}. HMRS (EI): *m/z* calcd. for $C_{22}H_{34}O_4Si$ 390.2226; found 390.2220.

Alcohol 19: Tetrabutylammonium fluoride (30 mL, 30 mmol, 1 M solution in THF) was added to neat diene **23** (1.62 g, 4.17 mmol). The reaction mixture was stirred at room temperature for 48 h, diluted with Et_2O (200 mL), washed with saturated aqueous ammonium chloride solution (50 mL) and brine (50 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/EtOAc, 9:1 to 7:3) to give alcohol **19** (1.1 g, 3.98 mmol, 95%) as a slightly yellow solid. R_f = 0.3 (cyclohexane/EtOAc, 7:3). M.p. 59–60 °C. ^{1}H NMR: δ = 6.53 (s, 1 H), 6.36 (dd, *J* = 17.7, 10.8 Hz, 1 H), 6.06 (s, 1 H), 5.84–5.81 (m, 1 H), 5.48 (d, *J* = 17.7 Hz, 1 H), 5.05 (d, *J* = 10.8 Hz, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 2.67–2.29 (m, 5 H) ppm. ^{13}C NMR: δ = 152.6 (C), 151.2 (C), 140.9 (CH), 140.1 (C), 138.0 (C), 137.9 (C), 135.7 (CH), 126.9 (C), 110.0 (CH_2), 109.0 (CH), 62.0 (CH_3), 61.4 (CH), 60.8 (CH_3), 55.9 (CH_3), 31.4 (CH_2), 29.9 (CH_2) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3477, 2929, 2852, 1638, 1597 cm^{-1}. HMRS (EI): *m/z* calcd. for $C_{16}H_{20}O_4$ 273.1362; found 273.1353.

Representative Procedure for the Oxidative Rearrangement of Alcohol 19. Ketone 10: A solution of **19** (364 mg, 1.31 mmol) in dry CH_2Cl_2 (9 mL) was added dropwise at room temperature under argon to a suspension of PCC (560 mg, 2.74 mmol) and silica gel (560 mg) in dry CH_2Cl_2 (9 mL). The reaction mixture was stirred for 1 h and filtered through Florisil® with elution with Et_2O to give ketone **10** (200 mg, 0.73 mmol, 55%) as a yellow solid. R_f = 0.37 (cyclohexane/EtOAc, 8:2). M.p. 74–75 °C. ^{1}H NMR: δ = 7.64 (s, 1 H), 6.86 (dd, *J* = 17.3, 10.8 Hz, 1 H), 6.58 (s, 1 H), 5.63 (dd, *J* = 17.3, 1.3 Hz, 1 H), 5.22 (dd, *J* = 10.8, 1.3 Hz, 1 H), 3.93 (s, 3 H), 3.91 (s, 3 H), 3.87 (s, 3 H), 2.91–2.87 (m, 2 H), 2.83–2.79 (m, 2 H) ppm. ^{13}C NMR: δ = 200.8 (C), 154.4 (C), 153.9 (C), 140.6 (C), 138.6 (C), 135.6 (C), 135.3 (CH), 131.6 (CH), 121.6 (C), 115.2 (CH_2), 107.5 (CH), 61.8 (CH_3), 61.0 (CH_3), 56.1 (CH_3), 44.4 (CH_2), 29.8 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2938, 2838, 1663, 1590 cm^{-1}. HMRS (EI): *m/z* calcd. for $C_{16}H_{18}O_4$ 274.1205; found 274.1211.

Tricyclic Ketone 7: A solution of methyl propiolate (90 µL, 1 mmol) and ketone **10** (30 mg, 0.109 mmol) in toluene (400 µL) was heated in a sealed tube at 115 °C for 22 h. The volatiles were removed by evaporation under reduced pressure, and the residue was dissolved in dry CH_2Cl_2 (1 mL). DDQ (28 mg, 0.123 mmol) was added, and the mixture was stirred for 20 h. The solvent was then evaporated under reduced pressure, and the residue was filtered through a layer of Al_2O_3 with EtOAc in petroleum ether (25%) as eluent to give ketone **7** (33 mg, 0.092 mmol, 85%, 2 steps) as a white solid. R_f = 0.5 (EtOAc/petroleum ether, 1:2). M.p. 147–148 °C. ^{1}H NMR: δ = 8.01 (dd, *J* = 7.6, 1.4 Hz, 1 H), 7.60 (dd, *J* = 7.6, 1.4 Hz, 1 H), 7.46 (t, *J* = 7.6 Hz, 1 H), 6.62 (s, 1 H), 3.91 (s, 3 H), 3.84 (s, 3 H), 3.70 (s, 3 H), 3.34 (s, 3 H), 3.19 (td, *J* = 13.2, 5.2 Hz, 1 H), 3.03–2.86 (m, 2 H), 2.71 (dt, *J* = 13.6, 3.6 Hz, 1 H) ppm. ^{13}C NMR: δ = 206.7 (C), 168.2 (C), 153.5 (C), 151.9 (C), 141.4 (C), 141.1 (C), 134.4 (C), 134.1 (C), 132.5 (C), 132.4 (CH), 130.2 (CH), 127.6 (CH), 123.2 (C), 106.9 (CH), 61.1 (CH_3), 60.6 (CH_3), 56.0 (CH_3), 52.1 (CH_3), 48.6 (CH_2), 30.0 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2937, 2860, 1730, 1692, 1589 cm^{-1}. MS (CI, NH_3): *m/z* (%) = 325 (40), 357 $[M + 1]^{+\cdot}$ (100), 374 $[M + 18]^{+\cdot}$ (50). HMRS (EI): *m/z* calcd. for $C_{20}H_{20}O_6$ 356.1260; found 356.1267.

Diels–Alder Reaction of Diene 10. Cycloadduct 28: A solution of methyl β-nitroacrylate (**27**, 56 mg, 0.421 mmol) and ketone **10** (76 mg, 0.28 mmol) in CH_2Cl_2 (0.5 mL) was stirred at room temperature for 7.5 h. The volatiles were removed by evaporation under reduced pressure, and the residue was purified by chromatography on silica gel (EtOAc/petroleum ether, 1:2, then 1:1) to give **28** (111 mg, 0.274 mmol, 97%) as a colorless oil as a mixture of two diastereoisomers (4:1) separable by chromatography on silica gel. **Major Isomer:** ^{1}H NMR: δ = 6.42 (s, 1 H), 5.93 (q, *J* = 3.0 Hz, 1 H), 5.15 (t, *J* = 9.4 Hz, 1 H), 4.63 (dq, *J* = 9.4, 3.0 Hz, 1 H), 3.83

(s, 3 H), 3.76 (s, 3 H), 3.75 (s, 3 H), 3.69 (s, 3 H), 3.66 (td, J = 9.4, 7.2 Hz, 1 H), 3.29–3.23 (m, 1 H), 2.82 (dtd, J = 18.4, 6.8, 2.4 Hz, 1 H), 2.78–2.67 (m, 2 H), 2.63–2.54 (m, 2 H) ppm. ^{13}C NMR: δ = 205.6 (C), 172.1 (C), 153.6 (C), 153.3 (C), 142.9 (C), 140.4 (C), 136.2 (C), 124.5 (CH), 117.6 (C), 107.7 (CH), 86.4 (CH), 60.9 (CH_3), 60.5 (CH_3), 55.8 (CH_3), 52.5 (CH_3), 45.2 (CH_2), 43.6 (CH), 39.2 (CH), 29.5 (CH_2), 27.1 (CH_2) ppm. **Minor Isomer:** ^{1}H NMR: δ = 6.36 (s, 1 H), 6.06 (q, J = 3.2 Hz, 1 H), 5.68 (dd, J = 5.2, 2.8 Hz, 1 H), 4.54–4.50 (m, 1 H), 3.97 (s, 3 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.59–3.50 (m, 1 H), 3.42–3.40 (m, 1 H), 2.90–2.71 (m, 3 H), 2.60–2.47 (m, 2 H) ppm. ^{13}C NMR: δ = 207.8 (C), 170.9 (C), 153.2 (C), 152.4 (C), 140.8 (C), 140.7 (C), 137.4 (C), 125.6 (CH), 118.0 (C), 108.5 (CH), 83.4 (CH), 61.1 (CH_3), 60.7 (CH_3), 55.8 (CH_3), 52.9 (CH_3), 44.6 (CH_2), 41.1 (CH), 36.1 (CH), 29.3 (CH_2), 23.1 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2953, 2856, 1743, 1708, 1594, 1556 cm^{-1}. MS (CI, NH_3): m/z (%) = 423 [M + 18]$^{+\cdot}$ (100). HMRS (EI): m/z calcd. for $C_{20}H_{23}O_6N$ 405.1423; found 405.1431.

Methyl Ester 8: DBU (80 µL, 0.5 mmol) was added to a solution of **28** (104 mg, 0.256 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature under N_2 for 4 h. The volatiles were removed in vacuo, and the residue was filtered through a thin plug of silica gel (EtOAc/petroleum ether, 1:3) to give, after solvent evaporation, 76 mg of elimination product. This was dissolved in CH_2Cl_2 (2 mL), and DDQ (90 mg, 0.40 mmol) was added. The solution was stirred at room temperature for 2 weeks. The solvent was evaporated, and the crude mixture was filtered through a layer of Al_2O_3 (25% EtOAc in petroleum ether) to give, after solvent removal, ester **8** (45 mg, 0.126 mmol, 50%) as a colorless oil. R_f = 0.3 (EtOAc/petroleum ether, 1:2). ^{1}H NMR: δ = 8.24 (d, J = 1.6 Hz, 1 H), 8.02 (dd, J = 8.0, 1.6 Hz, 1 H), 7.59 (d, J = 8.0 Hz, 1 H), 6.61 (s, 1 H), 3.94 (s, 1.5 H), 3.96 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.59 (s, 3 H), 3.10–2.80 (m, 3 H), 2.70 (br d, J = 9.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 206.4 (C), 166.5 (C), 153.5 (C), 152.2 (C), 143.0 (C), 141.6 (C), 135.5 (C), 134.2 (C), 132.6 (CH), 131.9 (C), 128.2 (CH), 127.6 (CH), 123.4 (C), 107.0 (CH), 61.24 (CH_3), 61.10 (CH_3), 56.0 (CH_3), 52.4 (CH_3), 47.9 (CH_2), 29.9 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2944, 2860, 1728, 1691, 1595 cm^{-1}. MS (CI, NH_3): m/z (%) = 357 [M + 1]$^{+\cdot}$ (70), 374 [M + 18]$^{+\cdot}$ (100). HMRS (EI): m/z calcd. for $C_{20}H_{20}O_6$ 356.1260; found 356.1255.

Representative Procedure for the Reductive Amination of Ketone 7. (±)-Allocolchicine 4: A solution of ketone **7** (17 mg, 0.047 mmol), NH_4OAc (35 mg, 0.45 mmol), and $NaBH_3CN$ (3 mg, 0.047 mmol) in MeOH (300 µL) was heated in a sealed tube at 60 °C for 18 h. After the mixture had cooled to room temperature, concentrated HCl (0.35 mL) was added, and the mixture was vigorously stirred for 15 min. After that, water (0.6 mL) was added, and the mixture was extracted twice with Et_2O. The ethereal layers were combined and set aside, the aqueous layer was treated with NaOH (10%) and extracted once with CH_2Cl_2 and once with Et_2O. The organic layers were combined, dried with $MgSO_4$, and concentrated under reduced pressure to give the crude amine (12 mg), which was dissolved in CH_2Cl_2 (300 µL) and Ac_2O (25 µL). Pyridine (25 µL) was added dropwise to this solution, with stirring. After 45 min at room temperature, the mixture was quenched with water (1 mL). The aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were washed with HCl (10%), dried with $MgSO_4$, and concentrated under reduced pressure to give allocolchicine *rac*-**4** (13 mg, 0.032 mmol, 69% in two steps) as a white solid as a 2:1 mixture of atropoisomers in $CDCl_3$ solution. M.p. 206–209 °C. **Major Rotamer:** ^{1}H NMR: δ = 7.79 (dd, J = 7.2, 1.2 Hz, 1 H), 7.46–7.38 (m, 2 H), 6.59 (s, 1 H), 5.80 (d, J = 7.2 Hz, 1 H, NH), 4.73–4.68 (m, 1 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 3.68 (s, 3 H), 3.38 (s, 3 H), 2.54–2.48 (m, 1 H), 2.44–2.36 (m, 2 H), 2.05 (s, 3 H), 1.84–1.77 (m, 1 H) ppm. ^{13}C NMR: δ = 169.3 (C), 152.9 (C), 151.0 (C), 149.4 (C), 140.0 (C), 136.3 (C), 133.8 (C), 131.8 (C), 130.9 (C), 127.1 (CH), 125.4 (CH), 123.4 (CH), 123.4 (C), 107.2 (CH), 61.1 (CH_3), 60.8 (CH_3), 55.9 (CH_3), 51.9 (CH_3), 49.6 (CH), 39.0 (CH_2), 30.2 (CH_2), 23.2 (CH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2935, 2855, 1729, 1645, 1596 cm^{-1}. MS (CI, NH_3): m/z (%) = 368 [M – OMe]$^{+\cdot}$ (40), 400 [M + 1]$^{+\cdot}$ (100). HMRS (EI): m/z calcd. for $C_{22}H_{25}NO_6$ 399.1682; found 399.1689.

(±)-Allocolchicine 5: This compound was prepared from **8** according to the same procedure as for *rac*-**4**, to give *rac*-**5** (57%) as a white solid as a 2:1 mixture of atropoisomers in $CDCl_3$ solution. M.p. 181–183 °C. **Major Atropoisomer:** ^{1}H NMR: δ = 8.17 (d, J = 2.0 Hz, 1 H), 8.00 (dd, J = 8.0, 2.0 Hz, 1 H), 7.36 (d, J = 8.0 Hz, 1 H), 6.58 (s, 1 H), 5.82 (d, J = 7.6 Hz, 1 H, NH), 4.90–4.84 (m, 1 H), 3.95 (s, 3 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.56 (s, 3 H), 2.56–2.46 (m, 2 H), 2.30–2.23 (m, 1 H), 2.07 (s, 3 H), 1.86–1.80 (m, 1 H) ppm. ^{13}C NMR: δ = 169.2 (C), 167.2 (C), 153.1 (C), 151.3 (C), 144.2 (C), 141.4 (C), 134.7 (C), 134.5 (C), 131.5 (CH), 128.6 (C), 128.4 (CH), 124.1 (C), 122.4 (CH), 107.6 (CH), 61.3 (CH_3), 61.2 (CH_3), 56.1 (CH_3), 52.1 (CH_3), 49.5 (CH), 39.5 (CH_2), 30.3 (CH_2), 23.3 (CH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2934, 2855, 1723, 1687, 1596 cm^{-1}. MS (CI, NH_3): m/z (%) = 341 (10), 400 [M + 1]$^{+\cdot}$ (100). HMRS (EI): m/z calcd. for $C_{22}H_{25}NO_6$ 399.1682; found 399.1683.

Alcohol (+)-(7*R*)-30: The ketone **8** (42 mg, 0.117 mmol) was dissolved in a solution of L-(+)-TarB-NO_2 (0.5 M, 0.325 mmol, 0.65 mL) in THF under argon. The solution was stirred at room temperature for 15 min, and $NaBH_4$ (14.5 mg, 0.38 mmol) was then added to the ketone/L-(+)-TarB-NO_2 solution in a single portion, causing rapid gas evolution. The reaction mixture was stirred for 60 min and then slowly quenched with HCl (3 M), until gas evolution was no longer observed. The mixture was brought to pH = 12 with NaOH (3 M) and extracted with diethyl ether (3 × 5 mL). The combined ether extracts were washed with H_2O (2 × 5 mL) and dried with $MgSO_4$. The volatiles were removed in vacuo, and the residue was purified by chromatography on silica gel (EtOAc/petroleum ether, 1:4) to give (+)-**30** (36 mg, 0.100, 86%) as a colorless oil. HPLC (column: Chiralcel OD-H; *n*-heptane/propan-2-ol): 90% *ee*. $[a]_D^{25}$ = +20.0 [c = 0.46, $CHCl_3$, 90% *ee* (HPLC)]. R_f = 0.15 (EtOAc/cyclohexane, 3:7). ^{1}H NMR: δ = 8.11 (d, J = 1.8 Hz, 1 H), 8.03 (dd, J = 8.1, 1.8 Hz, 1 H), 7.75 (d, J = 8.1 Hz, 1 H), 6.59 (s, 1 H), 4.66 (dd, J = 9.3, 7.8 Hz, 1 H), 3.92 (s, 3 H), 3.912 (s, 3 H), 3.909 (s, 3 H), 3.66 (s, 3 H), 2.65–2.53 (m, 1 H), 2.47–2.41 (m, 1 H), 2.32–2.21 (m, 1 H), 2.10–2.07 (br. s, 1 H, OH), 1.98–1.88 (m, 1 H) ppm. ^{13}C NMR: δ = 167.3 (C), 153.1 (C), 150.9 (C), 146.8 (C), 141.2 (C), 135.5 (C), 133.3 (C), 131.1 (CH), 128.5 (C), 128.3 (CH), 123.7 (C), 122.8 (CH), 107.6 (C), 70.0 (CH), 61.0 (2 CH_3), 56.0 (CH_3), 52.0 (CH_3), 41.4 (CH_2), 30.3 (CH_2) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3488, 2937, 2858, 1719, 1598 cm^{-1}. HMRS (EI): m/z calcd. for $C_{20}H_{22}O_6$ 358.1416; found 358.1417.

Azide (–)-(7*S*)-31: Methanesulfonyl chloride (0.504 mL, 6.51 mmol) was added dropwise at 0 °C under argon to a solution of alcohol **30** (203 mg, 0.563 mmol) in dry pyridine (3.3 mL). The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 3 h and diluted with CH_2Cl_2 (30 mL). The organic phase was washed with aqueous saturated $CuSO_4$ solution (2 × 20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was diluted with dry DMF (5.6 mL), and NaN_3 (170 mg, 2.55 mmol) was added. The reaction mixture was warmed at 80 °C for 4 h, allowed to cool to room temperature, stirred at room temp. for 15 h, and diluted with CH_2Cl_2 (40 mL) and water (10 mL). The mixture was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water (2 × 10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc/petroleum ether, 1:4) to give azide **31** (155 mg, 0.404 mmol, 71%) as a colorless oil. $[\alpha]_D^{25}$ = –47.5 (*c* =1.03, $CHCl_3$). R_f = 0.55 (EtOAc/cyclohexane, 3:7). ^{1}H NMR: δ = 8.14 (d, *J* = 1.5 Hz, 1 H), 8.04 (dd, *J* = 8.4, 1.5 Hz, 1 H), 7.64 (d, *J* = 8.4 Hz, 1 H), 6.59 (s, 1 H), 4.48 (dd, *J* = 11.1, 6.6 Hz, 1 H), 3.931 (s, 3 H), 3.927 (s, 3 H), 3.918 (s, 3 H), 3.71 (s, 3 H), 2.62–2.44 (m, 2 H), 2.30–2.22 (m, 1 H), 2.06–1.97 (m, 1 H) ppm. ^{13}C NMR: δ = 167.0 (C), 162.5 (C), 153.4 (C), 151.0 (C), 142.1 (C), 141.4 (C), 134.6 (C), 134.2 (C), 131.4 (CH), 129.0 (C), 128.5 (CH), 123.8 (CH), 123.5 (C), 107.7 (CH), 61.0 (2 × CH_3 + CH), 56.0 (CH_3), 52.0 (CH_3), 38.8 (CH_2), 30.2 (CH_2) ppm. IR (neat): $\tilde{\nu}_{max}$ = 2929, 2856, 2102, 1721, 1598 cm^{-1}. HMRS (EI): *m*/*z* calcd. for $C_{20}H_{21}N_3O_5$ 383.1481; found 383.1483.

(–)-(7*S*)-Allocolchicine 5: 5% Pd/$CaCO_3$/3.5% Pb (10 mg) as catalyst was added to a solution of azide **31** (50 mg, 0.130 mmol) in absolute EtOH (3 mL). The flask was flushed with H_2, and a positive pressure of H_2 was maintained. The mixture was stirred at room temperature under 1 atm of H_2 for 20 h. The mixture was then filtered through a layer of Celite, the Celite was washed with acetone, and the solvents were removed under reduced pressure. The residue was dissolved in dry CH_2Cl_2 (0.6 mL), and then pyridine (0.3 mL) was added to the solution. Ac_2O (0.3 mL) was added dropwise to the stirred solution. After 1 h of stirring at room temperature, the mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc/cyclohexane, 1:9 to 7:3) to give (7*S*)-**5** (30.5 mg, 0.076 mmol, 58%) as a white solid. Recrystallization from a mixture of hexane and EtOAc. HPLC (column: Chiralcel OD-H; *n*-heptane/propan-2-ol) 93.6% *ee*. M.p. 177 °C. $[\alpha]_D^{20}$ –21.0 [*c* = 0.45, $CHCl_3$, 94% *ee* (HPLC)]. R_f = 0.5 (EtOAc/cyclohexane, 3:7).

Propargyl Silyl Ether 32: Ethynylmagnesium bromide (16 mL, 8.0 mmol, 0.5 M solution in THF) was added dropwise at 0 °C under argon to a solution of aldehyde **14** (2.00 g, 7.08 mmol) in dry THF (10 mL). The reaction mixture was stirred at 0 °C for 3 h, saturated aqueous ammonium chloride solution (10 mL) was added, and the mixture was diluted with Et_2O (50 mL). The biphasic mixture was allowed to warm to room temperature and separated, and the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give the crude propargyl alcohol. This crude propargyl alcohol was immediately dissolved in dry DMF (6.4 mL). Imidazole (1.44 g, 21.17 mmol) and *tert*-butyldimethylsilyl chloride (3.20 g, 21.27 mmol) were added at room temperature under argon, and the mixture was stirred for 18 h. The reaction mixture was diluted with Et_2O (100 mL), washed with HCl solution (1.2 M, 50 mL), H_2O (50 mL), and brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/EtOAc, 9:1) to give propargyl silyl ether **32** (2.83 g, 6.69 mmol, 81%) as a colorless oil. R_f = 0.32 (EtOAc/cyclohexane, 3:7). ^{1}H NMR: δ = 6.56 (s, 1 H), 6.03 (d, *J* = 2.4 Hz, 1 H), 3.86 (s, 3 H), 3.83 (s, 6 H), 3.69 (s, 3 H), 3.46–3.36 (m, 2 H), 3.27–3.17 (m, 2 H), 2.48 (d, *J* = 2.4 Hz, 1 H), 0.88 (s, 9 H), 0.17 (s, 3 H), 0.07 (s, 3 H) ppm. ^{13}C NMR: δ = 173.8 (C), 153.0 (C), 150.6 (C), 140.1 (C), 136.7 (C), 125.7 (C), 109.8 (CH), 85.4 (C), 72.2 (CH), 61.6 (CH_3), 60.7 (CH_3), 57.4 (CH), 55.9 (CH_3), 51.4 (CH_3), 36.1 (CH_2), 27.8 (CH_2), 25.8 (3 CH_3), 18.1 (C), –4.9 (CH_3), –5.0 (CH_3) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3276, 2950, 2933, 2856, 2109, 1736, 1598 cm^{-1}. HMRS (EI): *m*/*z* calcd. for $C_{22}H_{34}O_6Si$ 422.2125; found 422.2131.

Aldehyde 33: A solution of $LiAlH_4$ (95 mg, 2.50 mmol) in THF (2.5 mL) was added dropwise under argon to a solution of ester **32** (610 mg, 1.44 mmol) in anhydrous THF (20 mL). The reaction mixture was stirred at –10 °C for 30 min and quenched by successive addition of H_2O (95 µL), NaOH solution (15%, 95 µL), and H_2O (285 µL). The solution was filtered, and the granular inorganic precipitate was rinsed with Et_2O (50 mL). The combined organic layers were concentrated under reduced pressure to give the crude alcohol (590 mg), which was used in the next step without further purification. This crude alcohol (590 mg) was dissolved in dry CH_2Cl_2 (17 mL). PDC (1.652 g, 4.38 mmol) was added at room temperature under argon, and the mixture was stirred for 24 h. The reaction mixture was diluted with Et_2O (100 mL) and filtered through Florisil®, and the Florisil® was rinsed with Et_2O. The filtrate was concentrated under reduced pressure to give aldehyde **33** (450 mg, 1.15 mmol, 79%) as a colorless oil. R_f = 0.23 (EtOAc/cyclohexane, 1:4). ^{1}H NMR: δ = 9.83 (t, *J* = 0.9 Hz, 1 H), 6.53 (s, 1 H), 6.05 (d, *J* = 2.4 Hz, 1 H), 3.86 (s, 3 H), 3.83 (s, 6 H), 3.46–3.36 (m, 1 H), 3.30–3.20 (m, 1 H), 2.87–3.81 (m, 2 H), 2.50 (d, *J* = 2.4 Hz, 1 H), 0.88 (s, 9 H), 0.17 (s, 3 H), 0.07 (s, 3 H) ppm. ^{13}C NMR: δ = 202.0 (C), 153.0 (C), 150.5 (C), 140.0 (C), 136.5 (C), 125.6 (C), 109.7 (CH), 85.3 (C), 72.8 (CH), 61.6 (CH_3), 60.7 (CH_3), 57.3 (CH), 55.8 (CH_3), 45.8 (CH_2), 25.7 (3 CH_3), 24.9 (CH_2), 18.1 (C), –4.8 (CH_3), –5.1 (CH_3) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3281, 2930, 2857, 2717, 2112, 1724, 1597 cm^{-1}. HMRS (EI): *m*/*z* calcd. for $C_{21}H_{32}O_5Si$ 392.2019; found 392.2000.

Aldehyde 34: Potassium *tert*-butoxide (1.025 g, 9.13 mmol) was added under argon at 10 °C to a solution of (methoxymethyl)triphenylphosphonium chloride (3.47 g, 10.09 mmol) in dry THF (40 mL). The resulting orange-red solution was stirred at room temperature for 45 min and then cooled to 15 °C; a solution of aldehyde **33** (973 mg, 2.48 mmol) in dry THF (11 mL) solution was added dropwise under argon to the resulting ylide solution, which was maintained at 15 °C. The reaction mixture was stirred at room temperature for 1 h, and water (20 mL) was added. The biphasic mixture was separated, and the aqueous phase was extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/EtOAc, 9:1) to give the alkene (861 mg, 2.05 mmol, 82%) as a colorless oil. This alkene was dissolved in Et_2O (79 mL). An aqueous solution of $HClO_4$ (7%, 27 mL) was added, and the biphasic mixture was stirred at room temperature for 36 h. The biphasic mixture was separated, and the aqueous phase was extracted with Et_2O (3 × 75 mL). The combined organic extracts were washed with saturated aqueous sodium hydrogencarbonate solution (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/EtOAc, 4:1) to give aldehyde **34** (470 mg, 1.15 mmol, 47%) as a colorless oil. R_f = 0.26 (cyclohexane/EtOAc, 4:1). ^{1}H NMR: δ = 9.81 (t, *J* = 1.5 Hz, 1 H), 6.57 (s, 1 H), 6.04 (d, *J* = 2.1 Hz, 1 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.11–2.90 (m, 2 H), 2.53 (dt, *J* = 7.2, 1.5 Hz, 1 H), 2.47 (d, *J* = 2.1 Hz, 1 H), 2.07–1.96 (m, 1 H), 0.88 (s, 9 H), 0.18 (s, 3 H), 0.05 (s, 3 H) ppm. ^{13}C NMR: δ = 202.3 (C), 152.9 (C), 150.6 (C), 139.9 (C), 137.4 (C), 125.5 (C), 109.5 (CH), 85.6 (C), 72.4 (CH), 61.6 (CH_3), 60.7 (CH_3), 57.3 (CH), 55.9 (CH_3), 43.9 (CH_2), 31.7 (CH_2), 25.7 (3 CH_3), 23.9 (CH_2), 18.1 (C), –4.9 (CH_3), –5.1 (CH_3) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3299, 2934, 2857, 2720, 2109, 1725, 1597 cm^{-1}. HMRS (EI): *m*/*z* calcd. for $C_{22}H_{34}O_5Si$ 406.2176; found 406.2178.

Enyne 35: *n*-Butyllithium (2.9 mL, 4.64 mmol, 1.6 M solution in hexane) was added dropwise under argon at room temperature to a solution of methyltriphenylphosphonium bromide (1.64 g, 4.60 mmol) in dry THF (12 mL). The resulting yellow-orange solution was stirred at room temperature for 45 min and cooled to 15 °C; a solution of aldehyde **34** (470 mg, 1.15 mmol) in dry THF (12 mL) was added dropwise under argon to the resulting ylide solution, which was maintained at 15 °C. The reaction mixture was stirred at room temperature for 30 min, and water (20 mL) was added. The biphasic mixture was separated, and the aqueous phase was extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/EtOAc, 95:5 to 9:1) to give enyne **35** (286 mg, 0.70 mmol, 61%) as a colorless oil. R_f = 0.45 (EtOAc/cyclohexane, 1:9). ^{1}H NMR: δ = 6.56 (s, 1 H), 6.04 (d, J = 2.4 Hz, 1 H), 5.95–5.82 (m, 1 H), 5.05 (qd, J = 17.1, 1.5 Hz, 1 H), 4.97 (br. d, J = 9.9 Hz, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.08–2.85 (m, 2 H), 2.47 (d, J = 2.4 Hz, 1 H), 2.21 (q, J = 6.9 Hz, 2 H), 1.82–1.71 (m, 2 H), 0.90 (s, 9 H), 0.20 (s, 3 H), 0.07 (s, 3 H) ppm. ^{13}C NMR: δ = 152.8 (C), 150.6 (C), 139.7 (C), 138.8 (CH), 138.6 (C), 125.5 (C), 114.4 (CH_2), 109.5 (CH), 85.6 (C), 72.3 (CH), 61.6 (CH_3), 60.7 (CH_3), 57.4 (CH), 55.8 (CH_3), 34.2 (CH_2), 30.9 (CH_2), 25.8 (3 CH_3), 18.1 (C), –4.8 (CH_3), –5.0 (CH_3) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3306, 2954, 2928, 2857, 1641, 1597 cm^{-1}. HMRS (EI): m/z calcd. for $C_{23}H_{36}O_4Si$ 404.2383; found 404.2376.

RCM of 35. Alcohol 36: Grubbs catalyst II (**17**, 87 mg, 10 mol-%) was added under argon to a degassed solution of enyne **35** (249 mg, 0.61 mmol) in dry CH_2Cl_2 (250 mL). The mixture was heated at reflux for 4 h. The solvent was removed, and the residue was subjected to flash chromatography on silica gel (EtOAc/cyclohexane, 5:95) to give the protected diene (236 mg, 0.58 mmol, 95%) as a colorless oil. R_f = 0.54 (EtOAc/cyclohexane, 1:9). ^{1}H NMR: δ = 6.43 (s, 1 H), 6.32 (dd, J = 17.4, 10.8 Hz, 1 H), 5.92 (s, 1 H), 5.83 (t, J = 7.5 Hz, 1 H), 5.35 (dd, J = 17.4, 1.2 Hz, 1 H), 5.02 (d, J = 10.8 Hz, 1 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 3.75 (s, 3 H), 3.56–3.46 (m, 1 H), 2.50 (dd, J = 12.9, 5.1 Hz, 1 H), 1.84–1.71 (m, 2 H), 1.64–1.48 (m, 2 H), 0.75 (s, 9 H), 0.06 (s, 3 H), –0.05 (s, 3 H) ppm. ^{13}C NMR: δ = 152.9 (C), 151.2 (C), 143.1 (C), 141.1 (CH), 139.7 (C), 139.4 (C), 128.9 (CH), 127.5 (C), 111.6 (CH_2), 109.0 (CH), 65.5 (CH), 61.9 (CH_3), 60.9 (CH_3), 55.9 (CH_3), 30.5 (CH_2), 29.8 (CH_2), 25.7 (3 CH_3), 23.1 (CH_2), 18.1 (C), –5.0 (CH_3), –5.3 (CH_3) ppm. IR (film): $\tilde{\nu}_{max}$ = 2925, 2854, 1632, 1595 cm^{-1}. Tetra-*n*-butylammonium fluoride (4.8 mL, 1 M solution in THF) was added to a solution of the preceding diene (236 mg, 0.58 mmol) in THF (0.5 mL). The reaction mixture was stirred for 72 h at room temperature and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (cyclohexane/EtOAc, 4:1 then 7:3) to give alcohol **36** (148 mg, 0.51 mmol) as a colorless oil (84% from **35**). R_f = 0.23 (cyclohexane/EtOAc, 8:2). ^{1}H NMR: δ = 6.46 (s, 1 H), 6.38 (dd, J = 17.4, 10.8 Hz, 1 H), 6.02 (s, 1 H), 5.80 (t, J = 7.5 Hz, 1 H), 5.46 (dd, J = 17.4, 1.2 Hz, 1 H), 5.08 (d, J = 10.8 Hz, 1 H), 3.834 (s, 3 H), 3.831 (s, 3 H), 3.82 (s, 3 H), 3.24 (dt, 1 H), 2.65 (td, J = 12.9, 5.1 Hz, 1 H), 1.93–1.86 (m, 1 H), 1.76–1.57 (m, 3 H) ppm. ^{13}C NMR: δ = 152.9 (C), 151.5 (C), 142.6 (C), 140.0 (CH), 139.9 (C), 137.8 (C), 130.1 (CH), 126.7 (C), 112.1 (CH_2), 109.4 (CH), 64.9 (CH), 61.8 (CH_3), 60.7 (CH_3), 55.8 (CH_3), 30.8 (CH_2), 29.4 (CH_2), 23.8 (CH_2) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3492, 3086, 2935, 2849, 1631, 1595 cm^{-1}. HMRS (EI): m/z calcd. for $C_{17}H_{22}O_4$ 288.1518; found 288.1507.

Ketone 37: This compound was prepared from **36** by the same procedure as for **10** (76%), as a yellow oil. R_f = 0.64 (cyclohexane/EtOAc, 7:3). ^{1}H NMR: δ = 7.54 (s, 1 H), 6.84 (dd, J = 17.3, 10.8 Hz, 1 H), 6.56 (s, 1 H), 5.58 (dt, J = 17.3, 1.2 Hz, 1 H), 5.22 (dt, J = 17.3, 1.2 Hz, 1 H), 3.93 (s, 3 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 2.65 (t, J = 6.3 Hz, 2 H), 2.46 (t, J = 6.3 Hz, 1 H), 2.10–2.03 (m, 2 H) ppm. ^{13}C NMR: δ = 203.2 (C), 154.6 (C), 152.9 (C), 140.2 (C), 137.7 (C), 137.3 (C), 135.2 (CH), 132.5 (CH), 123.2 (C), 115.5 (CH_2), 108.2 (CH), 61.3 (CH_3), 60.8 (CH_3), 55.9 (CH_3), 38.0 (CH_2), 32.8 (CH_2), 32.5 (CH_2) ppm. IR (film): $\tilde{\nu}_{max}$ = 2933, 2854, 1654, 1620, 1591 cm^{-1}. HMRS (EI): m/z calcd. for $C_{17}H_{20}O_4$ 288.1362; found 288.1358.

Tricyclic Ketone 9: This compound was prepared from **37** according to the same procedure as for **8**. **Diels–Alder Reaction of Diene 37. Cycloadduct 38:** This compound was obtained from **37** (92%) as a white solid. M.p. 67–69 °C. ^{13}C NMR: δ = 204.3 (br. s, 1 C), 171.8 (C), 153.5 (C), 152.4 (C), 143.7 (C), 141.2 (br. s, 1 C), 136.8 (br. s, 1 C), 124.0 (br. s, 1 C), 121.0 (CH), 109.0 (CH), 86.0 (br. s, CH), 60.6 (CH_3), 59.9 (br. s, CH_3), 55.7 (CH_3), 52.4 (CH_3), 44.0 (br. s, CH_2), 42.3 (br. s, CH), 40.2 (br. s, CH), 34.8 (br. s, CH_2), 29.4 (br. s, CH_2), 26.8 (CH_2) ppm. IR (neat): $\tilde{\nu}_{max}$ = 2925, 2853, 1736, 1691, 1652, 1596, 1551 cm^{-1}. **Ketone 9:** DBU (160 µL, 1 mmol) was added to a solution of **38** (203 mg, 0.48 mmol) in THF (6.28 mL). The reaction mixture was stirred at room temperature under argon for 4.5 h. The volatiles were removed in vacuo, and the residue was purified by chromatography on silica gel (EtOAc/cyclohexane, 1:4 to 3:7) to give ketone **9** (75 mg, 0.20 mmol, 41%) as a colorless oil and alcohol **39** (88 mg, 0.23 mmol, 49%) as a white solid. **9:** R_f = 0.33 (EtOAc/cyclohexane, 3:7). ^{1}H NMR: δ = 8.17 (d, J = 8.7 Hz, 1 H), 8.04 (dd, J = 8.7, 1.8 Hz, 1 H), 7.97 (d, J = 1.8 Hz, 1 H), 6.55 (s, 1 H), 3.94 (s, 3 H), 3.934 (s, 3 H), 3.932 (s, 3 H), 3.61 (s, 3 H), 2.66–2.40 (m, 4 H), 2.12–2.00 (m, 1 H), 1.82–1.75 (m, 1 H) ppm. ^{13}C NMR: δ = 202.2 (C), 166.4 (C), 154.1 (C), 151.3 (C), 141.7 (C), 141.1 (C), 136.5 (C), 135.1 (CH), 134.8 (C), 132.5 (C), 129.0 (CH), 127.8 (CH), 126.7 (C), 107.1 (CH), 61.1 (2 × CH_3), 56.1 (CH_3), 52.3 (CH_3), 40.1 (CH_2), 31.0 (CH_2), 27.8 (CH_2) ppm. IR (neat): $\tilde{\nu}_{max}$ = 2927, 2854, 1724, 1670, 1643, 1595 cm^{-1}. HMRS (EI): m/z calcd. for $C_{21}H_{22}O_6$ 370.1416; found 370.1402. **39:** R_f = 0.15 (EtOAc/cyclohexane, 3:7). M.p. 118–119 °C. ^{1}H NMR: δ = 8.06 (d, J = 8.1, 1.5 Hz, 1 H), 7.91 (d, J = 1.5 Hz, 1 H), 7.80 (d, J = 8.1 Hz, 1 H), 6.55 (s, 1 H), 4.48 (d, J = 8.2 Hz, 1 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.64 (s, 3 H), 2.53 (dd, J = 13.4, 8.9 Hz, 1 H), 2.18–2.00 (m, 3 H), 1.85–1.60 (m, 2 H) ppm. ^{13}C NMR: δ = 167.1 (C), 153.5 (C), 150.5 (C), 150.4 (C), 140.3 (C), 138.9 (C), 133.6 (C), 131.6 (CH), 129.0 (CH), 127.9 (C), 124.7 (CH), 124.4 (C), 107.8 (C), 70.6 (CH), 61.0 (CH_3), 60.9 (CH_3), 55.9 (CH_3), 52.0 (CH_3), 38.8 (CH_2), 31.9 (CH_2), 27.6 (CH_2) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3479, 2934, 2858, 1720, 1596 cm^{-1}. HMRS (EI): m/z calcd. for $C_{21}H_{24}O_6$ 372.1573; found 372.1548.

(±)-Allocolchicine 6: This compound was prepared from **9** according to the same procedure as for compound *rac*-**4** (44%), as a white solid as a 2:1 mixture of atropoisomers in $CDCl_3$ solution. M.p. 156–158 °C. **Major Atropoisomer:** ^{1}H NMR: δ = 7.96 (dd, J = 8.0, 1.6 Hz, 1 H), 7.90 (d, J = 1.6 Hz, 1 H), 7.40 (d, J = 8.0 Hz, 1 H), 6.64 (s, 1 H), 5.53 (t, J = 7.6 Hz, 1 H), 5.04 (d, J = 7.6 Hz, 1 H, NH), 3.94 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.61 (s, 3 H), 2.65 (dd, J = 13.2, 7.6 Hz, 1 H), 2.18–1.45 (m, 5 H), 1.59 (s, 3 H) ppm. ^{13}C NMR: δ = 168.3 (C), 166.7 (C), 154.0 (C), 150.3 (C), 146.4 (C), 140.7 (C), 137.4 (C), 133.5 (C), 133.3 (CH), 129.8 (CH), 128.8 (CH), 126.1 (C), 124.0 (C), 108.2 (CH), 61.0 (CH_3), 60.5 (CH_3), 56.1 (CH_3), 53.1 (CH), 52.0 (CH_3), 32.6 (CH_2), 32.1 (CH_2), 25.4 (CH_2), 23.2 (CH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3437, 2995, 2935, 2855, 1724, 1685, 1593 cm^{-1}. HMRS (EI): m/z calcd. for $C_{23}H_{27}NO_6$ 413.1838; found 413.1831.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data for compounds **12a**, **12b**, **12c**, **12e**, **15**, **16**, and **18** and X-ray crystallographic data for compound **39**.

Acknowledgments

We gratefully thank Dr. X. Le Goff (DCPH, Ecole Polytechnique) for the X-ray structure determination of compound **39** and Mr. J.-P. Pulicani (DCSO, Ecole Polytechnique) for the determination of the optical purities of compounds **30** and (7*S*)-**5** by HPLC.

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[31] The X-ray structure of compound **39** and a short crystallographic summary can be found in the Supporting Information. CCDC-689496 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: June 19, 2008
Published Online: September 5, 2008

