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Diels−Alder Reaction−Aromatization Approach toward Functionalized Ring C Allocolchicinoids. Enantioselective Total Synthesis of (−)-7*S*-Allocolchicine

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Allocolchicinoids are analogues of the important antimitotic compound (−)-colchicine **1**. A strategy is reported for the synthesis of ring C functionalized allocolchicinoids, which is based on a Diels−Alder reaction−aromatization sequence. This route is complementary to the previously disclosed benzannulation approach involving Fischer carbene complexes and alkynes. Dienes **12** and **14** incorporate the natural substitution pattern on ring A and undergo Diels−Alder reactions with various dienophiles. Subsequent aromatization affords the set of differently functionalized ring C allocolchicinoids **15**−**19**, **23**, and **25**, with high regioselectively and in moderate to good yields. An intramolecular Diels−Alder reaction−aromatization sequence allows for access to allocolchicinoids with reversed regiochemical introduction of ring C substituents. The equilibria of the atropisomers of **15** and **19** are studied in three NMR solvents. Reactions of the dienes **12** and **14** with DMAD lead to the corresponding cycloadducts, but the subsequent aromatization is complicated. A regioselective Diels−Alder reaction−aromatization sequence is utilized as the key step in the first stereoselective total synthesis of (−)-allocolchicine **2**. Asymmetric introduction of hydroxy group at C7 is achieved by the enantioselective reduction of ketone **29.** The correct stereochemistry is then established by Mitsunobu inversion reaction using $Zn(N_3)_2$−2Py.

Introduction

(−)-Colchicine **1** (Figure 1), the major alkaloid from *Colchicum autumnale*, is one of the oldest known natural products.[1] It binds to the cytoskeletal protein tubulin, disrupting the microtubule-dependent functions in the cell and thereby suppressing the cell division process.[2] Similarly, active compounds with an aryl ring C, such as natural allocolchicine **2**, *N*-acetylcolchinyl-*O*-methyl ether **3**, and their derivatives,[3,4] are functional analogues of colchicine. Some other colchicine analogues with five-membered[5] and eight-membered[6] B rings, as well as allocolchicinoids with the functionality at C7 moved to C5,[7] have been recently prepared but found not to affect the tubulin polymerization process, despite their close structural similarity with the active allocolchicinoids. It was also shown that any alteration to the trioxygenated moiety of ring A leads to compounds with decreased tubulin-binding ability.[8] In contrast, the biological activity of ring C substituted allocolchicinoids varies with size, position, and nature of the substituents.[9,10] It was found that only natural (−)-7*S*-colchicine **1**, which adopts an a*R* biaryl configuration, but not its 7*R* enantiomer, binds effectively to tubulin. In solution, 7*S*-allocolchicinoids exist in equilibrium between a*R* (major) and a*S* (minor)

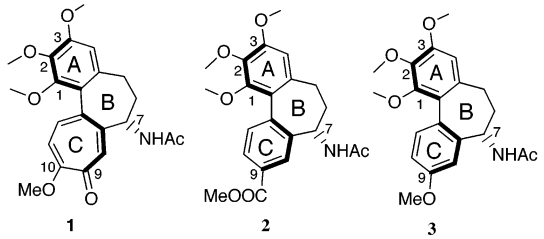

FIGURE 1. (−)-Colchicine and active allocolchicinoids.

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forms. Although the 7*R* enantiomer of allocolchicine **2** does not interfere with tubulin polymerization, several active 7*R* allocolchicinoids are known.[3] It is still not clear whether the a*R*,7*S* form or a small amount of the a*S*,7*S* form, present in equilibrium, is active in the tubulin-binding process.

Therefore, the preparation and biological evaluation of configurationally stable allocolchicinoids would be highly desirable. Very recently, three-dimensional quantitative structure−activity studies on colchicine analogues have been initiated,[11] demanding more such compounds with predictable variability of functionalization. To date, only a limited number of reports describe synthetic pathways toward the preparation of allocolchicinoids,[9,12] and the vast majority of these compounds are still being prepared from natural (−)-colchicine.

We have recently reported a strategy for the convergent[13] and stereoselective[14] construction of ring C functionalized allocolchicinoids based on the benzannulation reaction of correctly substituted Fischer carbene complexes with alkynes. However, since electron-deficient acetylenes are known to be sluggish partners in the benzannulation reaction,[15] a complementary approach was necessary to achieve the introduction of electron-withdrawing substituents on ring C of allocolchicinoids.

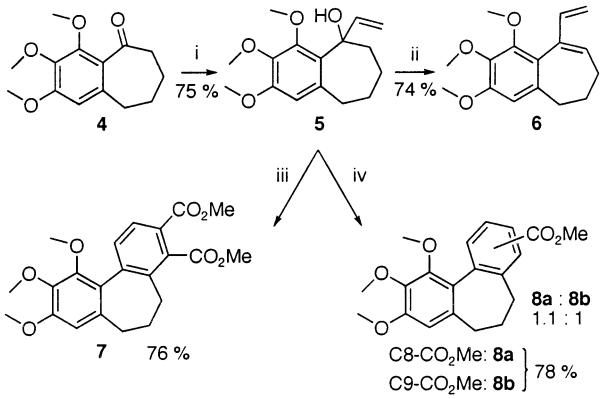
Results and Discussion

We present herein our results on the way to allocolchicinoids based on an approach that constructs the aromatic C-ring by a Diels−Alder reaction−aromatization sequence. The viability of this strategy is demonstrated by the preparation of differently substituted ring C allocolchicine analogues and by the first total synthesis of natural (−)-(7*S*)-allocolchicine.

Model Studies. Initial studies were carried out with diene **6**, which lacked the substituent at C7. This diene was prepared from the known benzosuberone **4** by the addition of vinylmagnesium bromide, followed by dehydration of the intermediate alcohol **5** (Scheme 1). The alcohol **5** was used as a convenient in situ source of diene **6** for the subsequent reactions. Thus, treatment of **5** with $MgSO_4$ and dimethyl acetylenedicarboxylate (DMAD) in refluxing benzene, followed by DDQ aromatization gave C7 unfunctionalized allocolchicinoid **7**.[16] Similar reaction of **5** with methyl propiolate was conducted at higher temperature (150 °C), using silica gel to induce dehydration. As expected, subsequent DDQ aromatization of the intermediate Diels−Alder adducts furnished almost equimolar mixture of regioisomers **8a** and **8b**.

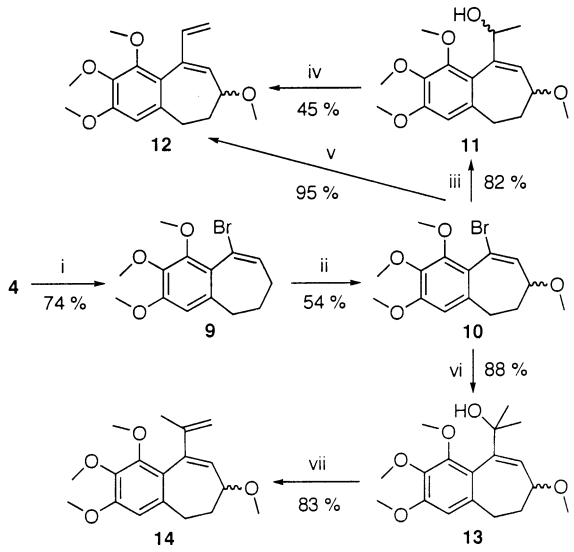
Synthesis of Dienes 12 and 14 Bearing the C7 Substituent. Preparation of the C7-functionalized diene **12** was envisioned starting from the bromide **10**, which can be prepared[14] from benzosuberone **4** via vinyl bromide **9** (Scheme 2). Metal−halogen exchange was performed using *t*-BuLi, and the resulting organolithium compound was immediately reacted with acetaldehyde, giving intermediate alcohols **11**. Dehydration of **11** using acidic reagents or $MgSO_4$ appeared problematic, since competing elimination of C7 functionality was possible under these conditions. Therefore, Burgess reagent ($Et_3N^+SO_2N^-CO_2Me$)[17] was chosen for the generation of diene **12**. Although **12** was thus obtained, the low yield of the overall transformation had prompted us to explore other options for its preparation. The shortcut from

SCHEME 1. Model Studies[a]



[a] Conditions: (i) (1) vinylMgBr, THF, 0 °C, 1 h, (2) H_2O/H^+; (ii) $MgSO_4$, benzene, reflux 2.5 h; (iii) (1) $MgSO_4$, DMAD, benzene, reflux 4 h, (2) DDQ, benzene, reflux 1 h; (iv) (1) silica gel, methyl propiolate, toluene, 150 °C, 14 h, (2) DDQ, benzene, reflux 1.5 h.

SCHEME 2. Synthesis of C7 Functionalized Dienes[a]



[a] Conditions: (i) (1) 2-bromo-1,3,2-benzodioxaphosphole, Br_2, CH_2Cl_2, rt, 30 min, (2) **4** in CH_2Cl_2, 0 °C, 30 min, rt, 15 min, (3) aq Na_2CO_3, 0 °C; (ii) (1) NBS, CCl_4, reflux, 20 min, (2) $NaHCO_3$, MeOH, rt, 12 h; (iii) (1) *t*-BuLi, ether −78 °C, 15 min, (2) CH_3CHO, −78 °C to rt, 1.5 h, (3) H_2O; (iv) $Et_3N^+SO_2N^-CO_2Me$, benzene, rt, 30 min, 50 °C, 30 min; (v) vinyl$SnBu_3$, 2% $PdCl_2$, 4% PPh_3, toluene, 80 °C, 3.5 h; (vi) (1) *t*-BuLi, ether −78 °C, 15 min, (2) $(CH_3)_2CO$, −78 °C to rt, 1 h, (3) H_2O; (vii) $MgSO_4$, benzene, reflux, 1.5 h.

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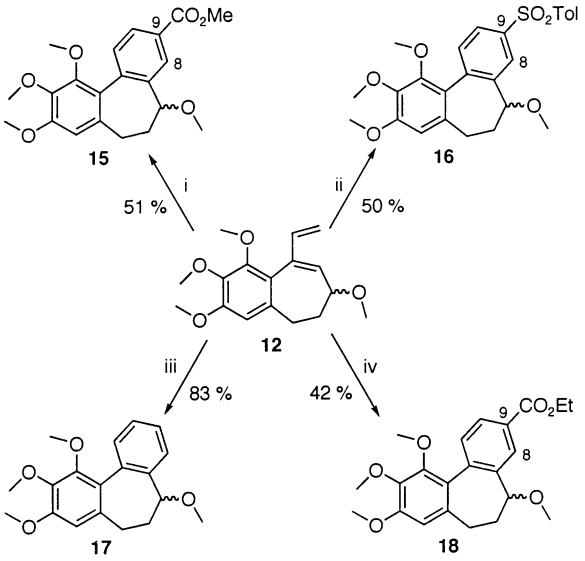
SCHEME 3. Diels–Alder Reactions of Diene 12[a]



[a] Conditions: (i) (1) methyl propiolate, toluene, 110 °C, 24 h, (2) DDQ, CH_2Cl_2, rt, 1 h; (ii) (1) TsCCH, toluene, 110 °C, 13 h, (2) DDQ, toluene, 110 °C, 9 h; (iii) (1) *trans*-$PhO_2SCH{=}CHSO_2Ph$, toluene, 140 °C, 15 h, (2) DBU, CH_2Cl_2, rt, 20 h; (iv) (1) *trans*-$O_2NCH{=}CHCO_2Et$, THF, 80 °C, 24 h, (2) DBU, THF, rt, 4 h, (3) DDQ, CH_2Cl_2, reflux, 2 h.

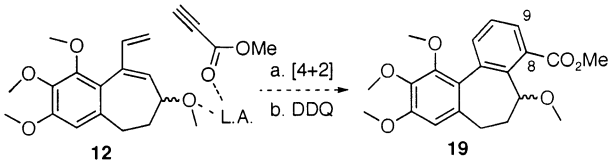
bromide **10** directly to diene **12** was taken by using the Stille coupling reaction,[18] which gives the diene in almost quantitative yield. Despite the known problems associated with the separation of the Stille coupling products from organotin byproducts, purification of **12** was achieved by a single column chromatography.

A similar approach was taken toward the synthesis of homologous diene **14**. Reaction of the vinyllithium, derived from **10** prepared according to the above procedure, with acetone afforded, after workup, the tertiary alcohol **13**. Dehydration of **13** proceeded smoothly, giving **14** in good overall yield. As was the case for **5**, alcohol **13** can also be used as an in situ source of diene **14** in the subsequent Diels–Alder reactions.

Reactions of Diene 12 with Various Dienophiles. Diels–Alder reaction of diene **12** with methyl propiolate was performed at 110 °C, giving the adducts, which were not isolated, but directly treated with DDQ. We were glad to discover that the reaction proceeded with complete regiocontrol, giving allocolchicinoid **15** as the only regioisomer (Scheme 3). It is likely that the steric interaction of the approaching dienophile with the C7 functionality in **12** was responsible for the regioselectivity, since similar reaction with the C7-unsubstituted diene **6** proceeded without any regiocontrol (Scheme 1). The substitution pattern of ring C in **15** matches that of allocolchicine and other active allocolchicinoids, thus opening the way toward their total synthesis.

The analogous reaction of diene **12** with tosylacetylene[19] proceeded at 110 °C to give, after DDQ aromatization, the tosyl-substituted product **16**, again with complete regiocontrol. Cycloaddition of **12** and *trans*-1,2-bis(phenylsulfonyl)ethylene[20] took place at 140 °C,

SCHEME 4. Attempted Reversal of Regiochemistry by Lewis Acid Participation



giving a mixture of Diels–Alder adducts. Upon treatment with DBU in CH_2Cl_2, elimination of both phenylsufonyl groups from these diastereomeric adducts can be achieved, leading to the single aromatized product **17** in high overall yield. Compounds **16** and **17** represent two new classes of allocolchicinoids, arylsulfonyl-substituted and unsubstituted on ring C, respectively. To the best of our knowledge, such compounds have never been prepared before. It is expected that their biological evaluation could help establish the role of ring C substituents in binding to tubulin.

It would also be important to explore the possibility of a regio-reversed Diels–Alder reaction–aromatization sequence, which would lead to the regioisomer of **15** and thus allow access to a new class of allocolchicinoids with substituents at C8 on ring C. We have envisioned that the use of ethyl β-nitroacrylate[21] would demonstrate the reversed regiochemistry[22] relative to methyl propiolate. As it was anticipated, this strong dienophile readily reacted with **12** at 80 °C, giving a mixture of Diels–Alder adducts. After the elimination of nitrous acid by DBU and the subsequent aromatization by DDQ one compound mobile on TLC was observed. It was isolated in moderate yield and identified as **18**. To our surprise, the carboxyethyl group in **18** was found to be in the C9 position, the same as the carboxymethyl group in **15**. Therefore, the regiochemistry of the cycloaddition was controlled by COOR group on the dienophile for reasons which are not completely understood at the moment.

We then attempted to reverse the regiochemistry of the cycloaddition of **12** and methyl propiolate by using different Lewis acidic additives (1 equiv), which were expected to coordinate to the C7 oxygen functionality of diene **12** and also to the oxygen of the dienophile. This should favor the regio-reversed products and therefore the formation of **19** upon aromatization (Scheme 4). Among the additives screened, the Lewis acids $FeCl_3$, $TiCl_4$, $SnCl_4$, $Zn(OTf)_2$. $Cu(OTf)_2$, $Sc(OTf)_3$, $Yb(OTf)_3$, and $La(OTf)_3$ led to the destruction of diene. Low conversion to cycloadducts with concomitant dienophile polymerization was observed with $Zr(O\text{-}i\text{-}Pr)_4$ and $Ti(O\text{-}i\text{-}Pr)_4$ as additives at 80 °C, but the regiochemistry of the product was found to be the same as that without the Lewis acid.

Since a regio-reversed Diels–Alder reaction could not be effected in an intermolecular fashion, we decided to pursue this goal via an intramolecular Diels–Alder reaction followed by aromatization and ring opening (Scheme 5). For this purpose, diene **21** was prepared from the corresponding bromide **20**[14] by Stille coupling in a manner analogous to that of the synthesis of **12** from **10**. Coupling of **21** and propiolic acid was performed in the

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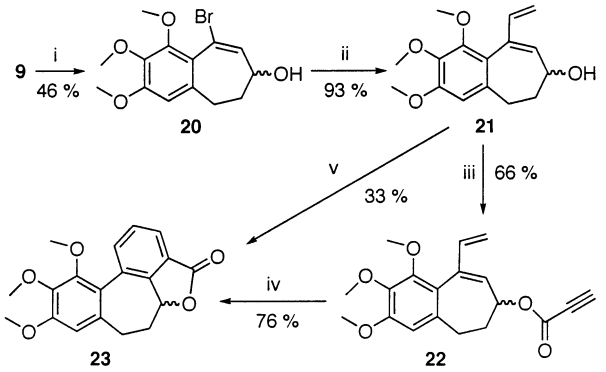
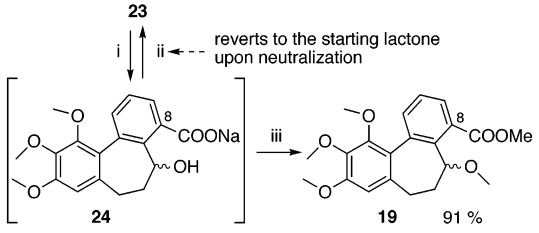
SCHEME 5. Preparation of Tetracyclic Lactone 23[a]



[a] Conditions: (i) (1) NBS, CCl_4, reflux, 20 min, (2) $NaHCO_3$, DME/H_2O, rt, 15 h; (ii) vinyl$SnBu_3$, 2% $PdCl_2$, 4% PPh_3, toluene, 80 °C, 4 h; (iii) propiolic acid, DCC, 10% DMAP, CH_2Cl_2, 0 °C, 10 min; (iv) (1) benzene, reflux, 60 h, (2) DDQ, benzene, rt, 1 h; (v) (1) propiolic acid, toluene, 85 °C, 20 h, (2) DDQ, toluene, rt, 2 h.

SCHEME 6. Ring Opening in Lactone 23[a]



[a] Conditions: (i) 50% aq NaOH, EtOH, reflux, 1.5 h; (ii) 10% aq HCl; (iii) (1) NaH (60% in oil), THF, reflux, 3 h, (2) Me_2SO_4, THF, reflux 15 h.

presence of DCC and DMAP,[23] giving the tethered substrate **22** in moderate yield. Intramolecular Diels–Alder reaction of **22** proceeded in refluxing benzene, giving after DDQ aromatization the expected tetracyclic lactone **23** in good yield. The only difficulty associated with the described procedure was the separation of **22** from dicyclohexylurea, which required repeated column chromatography. In an attempt to avoid the use of DCC, alcohol **21** was heated at 85 °C with propiolic acid in a "one-pot" approach to **23**. We have reasoned that the initial reaction between **21** and propiolic acid would afford **22** under these conditions, followed by the intramolecular Diels–Alder reaction of **22**. Indeed, the starting alcohol was consumed in 44 h, giving the mixture of adducts, which was cooled to room temperature and treated with DDQ. Lactone **23** was the only product isolated from the reaction mixture, albeit in the low yield, which is probably due to the partial polymerization of diene and dienophile during the reaction.

Opening of lactone ring in **23** was performed by ethanolic NaOH solution (Scheme 6). The intermediate sodium salt **24** did not give the corresponding carboxylic acid upon neutralization, but reverted to the starting lactone **23**. However, when **24** was thoroughly dried and methylated by NaH/Me_2SO_4, the expected allocolchicinoid **19** with the COOMe functionality at the C8 position was obtained.

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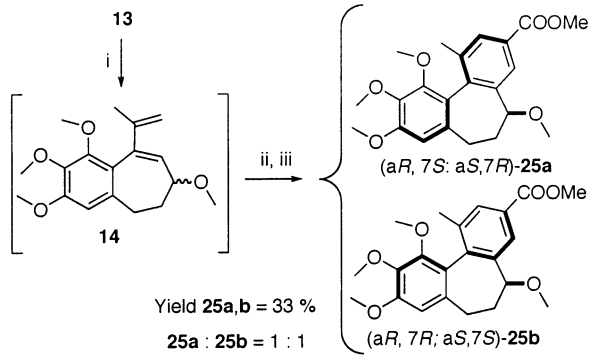
TABLE 1. Equilibrium of Rotamers of Allocolchicinoids 15 and 19 at Room Temperature

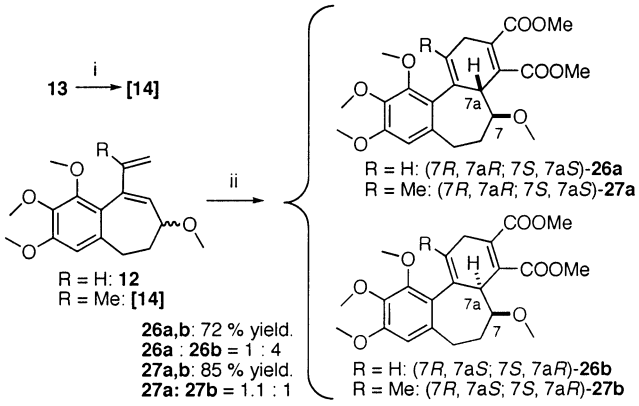
solvent	**15**	**19**
$CDCl_3$	10.5:1	2.5:1
C_6D_6	12.0:1	2.0:1
CD_3OD	12.7:1	2.9:1

SCHEME 7. Synthesis of Configurationally Stable Allocolchicinoids 25a,b[a]



[a] Conditions: (i) silica gel, toluene, 165 °C; (ii) methyl propiolate, toluene, 165 °C, 24 h; (iii) DDQ, benzene, reflux, 2 h.

SCHEME 8. Diels–Alder Reaction of Dienes 12, 14 with DMAD[a]



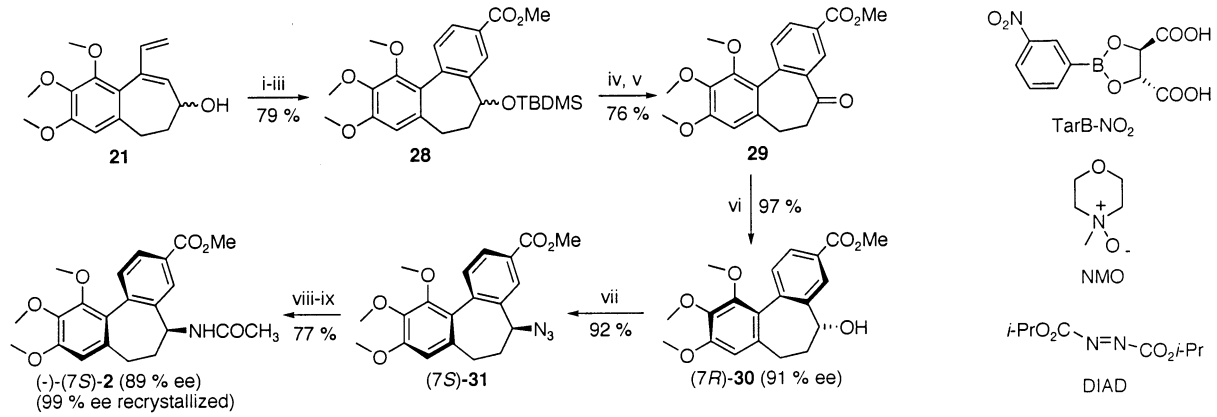
[a] Conditions: (i) silica gel, toluene, 110 °C; (ii) DMAD, toluene; R = H: 100 °C, 15 h; R = Me: 110 °C, 36 h.

As was mentioned in the Introduction, all known allocolchicinoids exist in a solvent-dependent equilibrium of rotameric forms. We have also observed such behavior for the analogue **15** and its regioisomer **19**. The ratio of the two atropisomeric forms was measured in three NMR solvents at room temperature (Table 1).

Contrary to previous observations with allocolchicine derivatives,[4] compounds **15** and **19** did not reveal a correlation between the solvent polarity and the atropisomeric ratio. Instead, the ratio strongly depended on the position of the CO_2Me group: the (a*R*,7*S*; a*S*,7*R*) isomer was clearly the favored one for **15**, whereas for **19** both isomers appeared in comparable amounts.

Preparation of Configurationally Stable Allocolchicinoids. For those allocolchicinoids that are substituted at C11, an equilibrium between the atropisomers would not be expected at room temperature. Synthetic access to this class of compounds proved possible via Diels–Alder reaction of diene **14**. The Diels–Alder reac-

SCHEME 9. Total Synthesis of (−)-(7*S*)-Allocolchicine 2[a]



[a] Conditions: (i) TBDMSCl, imidazole, DMF, rt, 15 h; (ii) methyl propiolate, toluene, 110 °C, 20 h; (iii) DDQ, CH_2Cl_2, rt, 3 h; (iv) TBAF−$3H_2O$, THF, rt, 1.25 h; (v) NMO−H_2O, 5% TPAP, MS 4 Å CH_2Cl_2, rt, 1 h; (vi) (1) TarB−NO_2 (0.4 M in THF), $LiBH_4$ (2 M in THF), (2) H_2O, H^+; (vii) Ph_3P, DIAD, $Zn(N_3)_2$−2Py, toluene, rt, 2 h; (viii) H_2, 5% Pd/$CaCO_3$/3.5% Pb, EtOH, rt., 30 h; (ix) Ac_2O, Py, CH_2Cl_2, rt, 0.5 h.

tion of diene **14**, generated in situ from **13**, proceeded with methyl propiolate at 165 °C, giving the intermediate cycloadducts. After DDQ aromatization two atropisomeric allocolchicinoids **25a**,**b** were isolated (Scheme 7). Analogous to the reaction of **12** described above, complete regiocontrol was also observed in this case, giving only C9-carboxymethyl derivatives. Unfortunately, the reaction showed no stereocontrol: **25a**,**b** were obtained as a 1:1 mixture. They could, however, be separated by column chromatography. The relative stereochemistry of **25a**,**b** was assigned by comparison of their ^{1}H NMR spectra with those of the known allocolchicinoids, whose structure had been previously secured by our group[14] and others[4] using X-ray crystallographic analysis. The isolation of the configurationally stable atropisomers **25a** and **25b** is an important step toward the understanding of the role of axial configuration in binding to tubulin. Allocolchicinoids **25a**,**b** will not undergo atropisomerization at room temperature and thus, it will be possible to separately evaluate their biological activity, revealing the effect of the axial configuration on binding. These evaluations are planned soon.

Diels−Alder Reactions of Dienes 12 and 14 with DMAD. The cycloaddition reaction between the isolated diene **12** and diene **14**, generated in-situ from **13**, with DMAD proceeded at 100−110 °C, giving the corresponding Diels−Alder adducts **26a**,**b** and **27a**,**b**, respectively (Scheme 8). Diastereomeric structures were tentatively assigned to **26a**,**b** and **27a**,**b** (shown) based on COSY and NOESY NMR experiments. To our surprise, aromatization with DDQ failed to give the expected allocolchicinoids, but rather generated mixtures of products with low mass balance.

Attempts to aromatize **26a**,**b** using *o*- and *p*-chloranil, Pd/C, C_2Cl_6/*t*-BuOK, and Br_2/CCl_4, then DBU also met with no success. The reason for such difficulties is not clear, since both **7** and **15** have been readily prepared by DDQ aromatization. Attempts are currently being made to overcome this limitation.

Total Synthesis of (−)-(7*S*)-Allocolchicine. Our synthetic approach involved the regioselective Diels−Alder reaction of methyl propiolate with a protected form of diene **21** as the key step (Scheme 9). We envisioned that the plan would include the generation of chiral nonracemic alcohol (7*R*)-**30** from ketone **29** by asymmetric reduction. The synthesis begins with the protection of the OH group in diene **21** with TBDMS. This group is supposed to function not only for protection purposes, but also as an important element of regiocontrol during the cycloaddition reaction. Indeed, the Diels−Alder reaction of the protected diene with methyl propiolate was complete in 20 h at 110 °C. Subsequent DDQ aromatization afforded the protected allocolchicinoid **28** as the only regioisomer in 79% yield. Deprotection by TBAF, followed by oxidation with *N*-methylmorpholine *N*-oxide (NMO) catalyzed by 5% tetrapropylammonium perruthenate (TPAP)[24] gave ketone **29** in 76% yield. Racemic (±)-**2** can be prepared from **29** by reductive amination followed by acetylation (50% yield, unoptimized). We expected that CBS reduction[25] of **29** would furnish (7*R*)-**30** in high yield and enantiomeric purity. However, a maximum of 70% ee could be obtained in the reduction of **29** with (*S*)-2-methyl-CBS-oxazaborolidine and even then only when employed in equimolar amounts. Kinetic resolution of racemic alcohol (±)-**30** by palladium-catalyzed air oxidation[26] proceeded with low selectivity (s = 2.9) and, therefore, is not synthetically useful. Fortunately, a recently developed asymmetric method for the reduction of ketones using TarB−NO_2[27] was found to afford alcohol (7*R*)-**30** in better enantiomeric purity. Thus, the reaction of **29** with 2 equiv of TarB−NO_2 and 2.1 equiv of $LiBH_4$ gave (7*R*)-**30** in 97% yield and 91% ee. Inversion of stereochemistry at C7 with concomitant introduction of the nitrogen functionality was achieved by Mitsunobu reaction with $Zn(N_3)_2$−2Py as azide source,[28] giving (7*S*)-**31** in 92% yield. Several methods were tested for the reduction of (7*S*)-**31** to the corresponding amine,[29] including PPh_3/H_2O;[29a] SmI_2;[29b] $FeSO_4$−$7H_2O/NH_3$;[29c] H_2 over 10% Pd/C,[29d] Pd/$CaCO_3$,[29e] PtO_2,[29f] Pd/$BaSO_4$, 5% Pd/

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$CaCO_3$/3.5% Pb. Heterogeneous hydrogenation over 5% Pd/$CaCO_3$/3.5% Pb was found to give the best results, affording after reduction and acetylation (−)-(7*S*)-allocolchicine **2** in 77% yield and 89% ee. The enantiomeric purity of **2** was improved to 99% ee by single recrystallization. Compound **2** showed identical physical properties with natural allocolchicine (mp, spectroscopic data).

Conclusions

Regioselective Diels−Alder reactions of the dienes incorporating the A and B rings of allocolchicines can be achieved with a variety of dienophiles leading, after aromatization, to the efficient construction of allocolchicinoids. This is used in the synthesis of allocolchicine analogues with natural substitution pattern on ring A and with controlled variability of functionalization on ring C. This strategy is complementary to the previously described benzannulation approach which works best in those cases where electron-releasing substituents on ring C are desired. The strategy developed in present work is used in the first stereoselective total synthesis of (−)-(7*S*)-allocolchicine, accomplished in 10 steps and 13% overall yield from benzosuberone **4**, which is readily available in large scale (4 steps, ∼53%) from 3,4,5-trimethoxybenzoic acid.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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