Total Synthesis

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# Enantioselective Synthesis of (+)-Mitomycin K by a Palladium-Catalyzed Oxidative Tandem Cyclization

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***Abstract:*** *The mitomycins, a family of bioactive natural products, feature a compact 6/5/5-fused polycyclic ring structure densely decorated with highly reactive and/or fragile quinone, amino ketal, and aziridine as well as carbamate moieties. It is this striking feature that has defeated numerous synthetic attempts towards these apparently small molecules, rendering them one of the most formidable targets for total synthesis. We herein report the first enantioselective synthesis of (+)-mitomycin K, a representative of G series mitomycins. The key step of this synthesis is an enantioselective oxidative cyclization catalyzed by a palladium/(+)-sparteine system that had previously been developed by our group. The robustness of this method bodes well for further applications in the asymmetric total synthesis of natural products, particularly those with characteristic 6/5/5-fused pyrroloindole skeletons.*

Mitomycins, especially mitomycin C (Figure 1), are well known for their potent DNA crosslinking activity,[1] which is concealed within the small and ostensibly simple structures. In fact, the total synthesis of these densely functionalized mitomycins[2] has challenged synthetic chemists for decades, mainly because of delicate functional group compatibility. Extensive synthetic studies[3] by Kishi and co-workers, who achieved the synthesis of both A and B series mitomycins (Figure 1) in racemic form during the 1970s, are well appreciated and considered as a milestone in total synthesis.[4] In the late 1980s, Fukuyama et al. capitalized on the so-called mitomycin rearrangement[5] to successfully develop two generations of remarkably short racemic syntheses towards A series mitomycins.[6] The only other two completed syntheses of mitomycins, which were reported by the groups of Danishefsky[7] and Jimenez[8] in the 1990s, led to racemic mitomycin K (Figure 1), a member of the G series. Aside from these achievements, various incomplete syntheses of mitomycins have been reported by over thirty groups.[2,9] However, to the best of our knowledge, an enantioselective synthesis of a mitomycin has not been achieved to date although enantiopure mitomycin C as well as its unnatural enantiomer were prepared by Fukuyama and co-workers by late-stage chemical resolution of a synthetic intermediate.[10] Interestingly, the unnatural enantiomer exhibited diminished cytotoxicity relative to the naturally occurring one,[11] highlighting the importance of the absolute configuration for their biological activity.

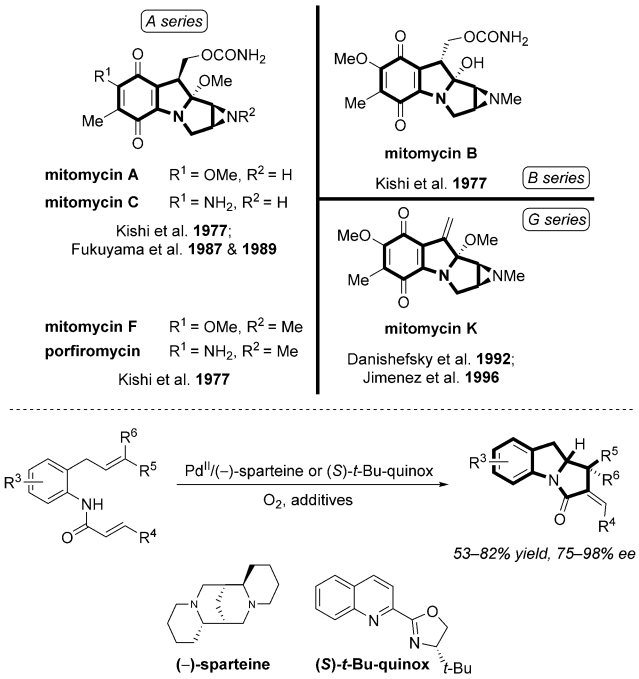


***Figure 1.*** Total synthesis of mitomycins.

Our group has recently developed two generations of enantioselective palladium-catalyzed oxidative tandem cyclization reactions (Figure 1)[12] that forge the basic 6/5/5-fused ring skeleton of mitomycins in either of the two enantiomeric forms with high enantiopurity in one step. In view of the synthetic potential of this method towards mitomycin synthesis, we were intrigued to realize the first enantioselective synthesis of a mitomycin. Herein, we disclose our efforts towards the first enantioselective synthesis of (+)-mitomycin K.

Our original retrosynthetic analysis is shown in Figure 2. Racemic azido alcohol **1** has previously been transformed into mitomycin K by Jimenez and Wang.[8] To access this intermediate from **2**, the C1 position should be activated for a regioselective azide substitution in the presence of a vicinal indole moiety, which would be present after A/B ring oxidation (from **2** to **1**). The oxidation removes the C9a chiral center, and thus the C1/C2 stereocenters should be formed in advance. Specifically, allylic hydroxylation of **3** followed by sequential oxidative cleavage of the exocyclic C=C double bond and reduction of the newly generated ketone would transfer the chirality from C9a to the C1 and C2

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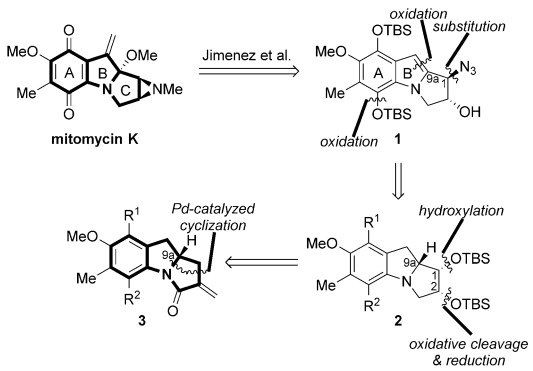
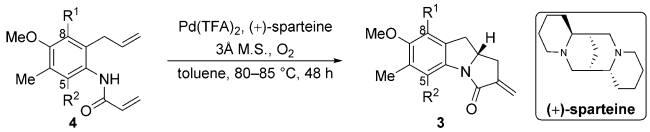



***Figure 2.*** Retrosynthetic analysis. TBS = *tert*-butyldimethylsilyl.

positions (from **3** to **2**). The configuration of the C9a carbon atom in **3** would be controlled by the judicious choice of an appropriate ligand enantiomer for the palladium-catalyzed cyclization.

In our previous work, substrates with a C5 substituent (see Table 1 for the C atom numbering), which would be vicinal to the reacting acrylamide moiety, were not examined. On the other hand, two substrates with C8 methyl groups adjacent to the reacting allyl motif were shown to be well suitable, affording the corresponding products with high enantioselectivity.[12a] Nonetheless, substitution at the C5 and C8 positions was thought to significantly affect the desired cyclization either sterically or electronically. In view of this, we initially prepared a small range of cyclization precursors that are all amenable to further manipulation towards **1** to explore the effect of the substitution pattern on the enantioselectivity (Table 1).[13] Interestingly, the enantioselectivity was first very low and then apparently dramatically increased in the other direction when the C5 substituent was changed from a bulky OBn group in **4a** to the medium-sized OMe group in **4b** and finally to a hydrogen atom in **4d**. In addition, the enantioselectivity was also significantly higher with substrate **4e** than with **4c**, which features an extra MeO group in the C5 position. With regard to substitution at the C8 position, the reactions of substrates **4c** and **4e** proceeded with higher enantioselectivity than those of **4b** and **4d**, respectively. Overall, these results indicate that C5 substitution is detrimental to the enantioselective cyclization while C8 substitution is somewhat beneficial. Although the reasons for these observations remain unclear for now,[14] this information is very instrumental for future applications of this method in natural product synthesis.

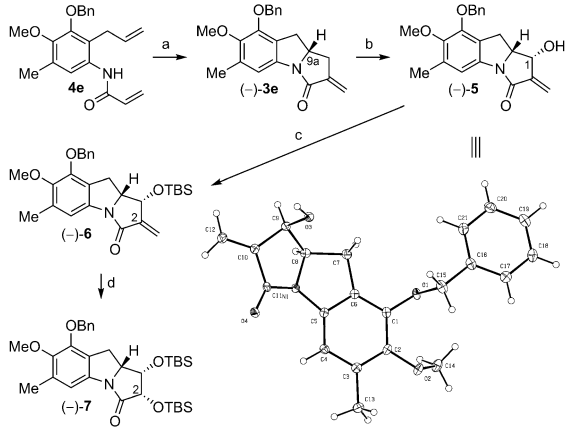
***Table 1:*** The effect of C5 and C8 substituents on the enantioselectivity.[a]




| Compound | $R^1$ | $R^2$ | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|
| **4a** | H | OBn | 24 | −23 |
| **4b** | H | OMe | 38 | 3 |
| **4c** | OBn | OMe | 30 | 28 |
| **4d** | H | H | 49 | 69 |
| **4e** | OBn | H | 47 | 83 |

[a] Reaction conditions: **4** (0.2 mmol), $Pd(TFA)_2$ (10 mol%), (+)-sparteine (40 mol%), 3 Å M.S. (100 mg), $O_2$ (1 atm), toluene (1.0 mL), 80–85 °C, 48 h. [b] Yields of isolated products. [c] Calculated by arbitrarily assigning the first peak in the chromatogram obtained by HPLC analysis on a chiral stationary phase to the *S* enantiomer for the equation: $ee = (R-S)/(R+S)$, which is not necessarily the case in reality. Bn = benzyl, M.S. = molecular sieves, TFA = trifluoroacetate.

We then began with the enantioselective synthesis of (+)-mitomycin K from enantioenriched (−)-**3e**, which was obtained in high yield from **4e** when the cyclization was conducted on gram scale (Scheme 1). Treatment of (−)-**3e** with selenium dioxide gave rise to allylic alcohol (−)-**5** with a diastereoselectivity of ≥10:1. The relative and absolute configurations of this compound were determined by X-ray crystal-structure analysis (Scheme 1).[15] The hydroxy group




***Scheme 1.*** Enantioselective and diastereoselective synthesis of amide (−)-**7**. Reagents and conditions: a) $Pd(TFA)_2$, (+)-sparteine, $O_2$, 3 Å M.S., toluene, 80–85 °C, 78%, 83% *ee*; b) $SeO_2$, 1,4-dioxane, 80–85 °C, ca. 56%, 83% *ee*, ≥10:1 d.r.; then recrystallization, ca. 48%, 94% *ee*, ≥50:1 d.r.; c) TBSOTf, 2,6-lutidine, DCM, 0 °C, 87%, 96% *ee*; d) $K_2OsO_4 \cdot 2H_2O$, NMO·$H_2O$, citric acid, *t*-BuOH, $H_2O$, RT; then $NaIO_4$, MeOH, $H_2O$, RT; then $NaBH_4$, MeOH, 0 °C; then TBSCl, DMAP, imidazole, DCM, RT, 70% over 4 steps, single diastereomer. DCM = dichloromethane, DMAP = 4-dimethylaminopyridine, NMO = *N*-methylmorpholine *N*-oxide, Tf = trifluoromethanesulfonyl.

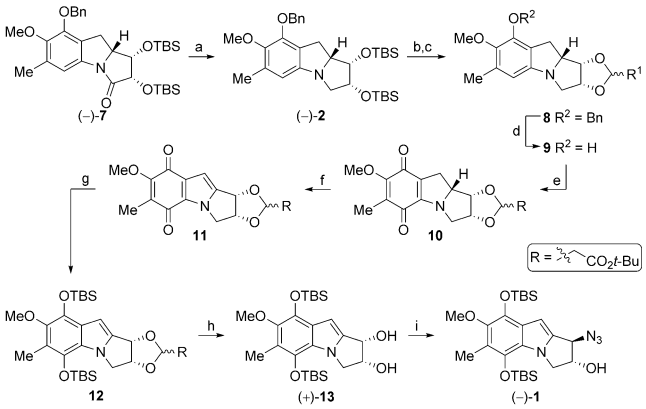
was found to occupy a pseudo-axial position, which is consistent with the preference for pseudo-axial hydroxylation of selenium dioxide reported by Trachtenberg and Carver.[16] The enantiopurity and diastereopurity were improved by recrystallization (94% *ee*, >50:1 d.r.). Alcohol (−)-**5**, which is unstable towards nucleophiles such as 4-dimethylaminopyridine,[17] was silylated with TBSOTf in the presence of the sterically hindered base 2,6-lutidine.

With the TBS-protected intermediate (−)-**6** in hand, the next task was to remove the exocyclic methylene group and construct the C2 chiral center (Scheme 1). As the electron-rich A ring may decompose under harsh ozonolysis conditions, mild methods for oxidative cleavage were explored. The citric acid promoted dihydroxylation of otherwise poorly

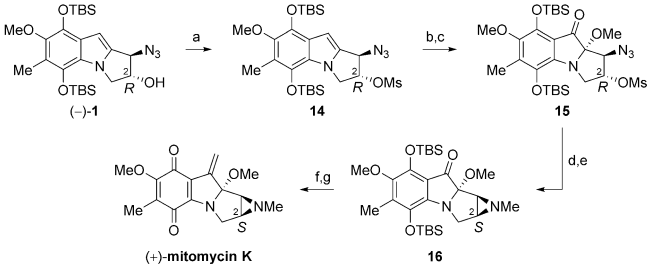
reactive α,β-unsaturated amides developed by Sharpless[18] and co-workers efficiently provided a diol intermediate. Subsequent straightforward diol cleavage, ketone reduction, and TBS alcohol deprotection yielded compound (−)-**7**, while the other diastereomer was not observed. Its relative configuration was established by 2D NMR spectroscopy.[13] The newly generated C2 alcohol was also converted into the corresponding Mosher esters,[19] which indicated that the C2 center is *S*-configured.[13] These results confirmed that no epimerization had occurred during these transformations.

In our proposed synthetic scheme (Figure 2), the A ring has to be decorated with two OTBS groups, such as those in **1**, and we surmised that the transformation of the diol into the azido alcohol should better be conducted after this manipulation. Thus a 2-(*tert*-butoxycarbonyl)ethylidene (Boc-ethylidene) protecting group was chosen to replace the existing TBS groups given its mild installation and basic deprotection conditions.[20] More importantly, this protecting group would not transform the C1 alcohol into a good leaving group, which might otherwise render this stereocenter fragile during future transformations considering the reductive activation mechanism of the mitomycins.[1] Accordingly, amide (−)-**7** was reduced with a borane tetrahydrofuran complex, and the TBS-protected diol (−)-**2** was then unmasked with tetra-*n*-butylammonium fluoride (Scheme 2). The Boc-ethylidene protecting group was installed onto the free diol under reported conditions[20] to afford a diastereomeric mixture of **8**. As the acetal chiral center is inconsequential, **8** was directly debenzylated by catalytic hydrogenolysis to afford phenol **9**. Whereas salcomine-catalyzed phenol oxidation with molecular oxygen led to decomposition of **9**,[17] the desired oxidation to quinone **10** was successful with Frémy's salt under argon atmosphere. Further dehydrogenation with DDQ delivered indoloquinone **11**. Surprisingly, the ensuing quinone reduction and hydroquinone protection failed[17] under conditions ($H_2$, Pd/C then TBSOTf[8b] or TMSOTf[21]) reported for structurally similar substrates for unknown reasons. Fortunately, sequential reduction of the quinone with sodium dithionite under biphasic conditions (dichloromethane/water) followed by TBS protection delivered **12** in high yield. The Boc-ethylidene protecting group was subsequently removed according to reported procedures.[20] The resulting free diol (+)-**13** was activated through the formation of a cyclic sulfite, which was opened by immediate treatment with sodium azide to provide azido alcohol (−)-**1** in 96% *ee* with a diastereoselectivity of about 8:1. The diastereoselectivity increased to > 50:1 when the diol was transformed into a thiocarbonate[22] for activation before the sodium azide treatment.




***Scheme 2.*** Enantioselective synthesis of (−)-**1**. Reagents and conditions: a) $BH_3$·THF, THF, reflux, 99%; b) TBAF, THF, RT, 69%; c) *tert*-butyl propiolate, DMAP, MeCN, RT, quantitative; d) $H_2$, Pd/C, EtOH, RT, 87%; e) Frémy's salt, $NaHCO_3$, acetone, $H_2O$, argon atmosphere, RT, 83%, 92% BRSM; f) DDQ, MeOH, RT, 86%; g) $Na_2S_2O_4$, $H_2O$, DCM, RT; then TBSCl, imidazole, DMAP, 3 Å M.S., DCM, RT, 71%, 85% BRSM; h) *n*-BuLi, pyrrolidine, THF, −78 to 0°C; then RT, 85%; i) $SO(im)_2$, THF, −10°C; then $NaN_3$, acetone, $H_2O$, RT, ca. 8:1 d.r., 78%, 96% *ee* or $CSCl_2$, DMAP, THF, −78°C to RT; then $NaN_3$, acetone, $H_2O$, RT, 75%, > 50:1 d.r. BRSM = based on recovered starting material, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, im = imidazolate, TBAF = tetra-*n*-butylammonium fluoride.

In Jimenez's 14 step racemic synthesis of mitomycin K,[8] this compound was next mesylated and oxidized[23] to introduce the C9a hydroxy group in a completely diastereoselective manner (Scheme 3). Subsequent methylation of the C9a hydroxy group,[23] azide reduction, spontaneous aziridination, Peterson olefination, and oxidation with PCC had furnished racemic mitomycin K. We followed the same route to obtain enantioenriched (+)-mitomycin K in seven steps from azido alcohol (−)-**1** with 97% *ee*. The C2 chiral center of the mitomycins has been reported to be derived from the C2 chiral center of D-glucosamine, presumably without any epimerization during biosynthesis.[2d] Thus *S* absolute configuration would be expected for all mitomycins, including mitomycin K. This hypothesis has previously been confirmed by X-ray crystal-structure analysis of mitomycin A–C.[24] In our current study, the absolute configuration of the C2 position in (−)-**1** was determined to be *R*[13] by Mosher ester analysis.[19] Subsequent alcohol activation and intramolecular $S_N2$ attack should in theory give rise to *S* configuration at the C2 position within the aziridine moiety, which is the same as that in naturally occurring mitomycin K. Therefore, we have completed the first enantioselective synthesis of mitomycin K in 33 overall steps from commercially available starting materials.[25]




***Scheme 3.*** Enantioselective synthesis of (+)-mitomycin K according to Jimenez's route. Reagents and conditions: a) MsCl, $Et_3N$, DCM, 0°C to RT, 90%; b) DMDO, AcOH, acetone, −30 to 0°C, 47%; c) NaH, $Me_2SO_4$, THF, 0°C, 76%; d) $Ph_3P$, $Et_3N$, THF, $H_2O$, RT; e) MeOTf, pyridine, DCM, 0°C, 54% over 2 steps; f) $TMSCH_2Li$, THF, −10°C; g) PCC, DCM, 0°C, 43% over 2 steps, 97% *ee*. DMDO = dimethyldioxirane, Ms = methanesulfonyl, PCC = pyridinium chlorochromate.

In conclusion, the asymmetric palladium-catalyzed cyclization reaction developed by our group has allowed us to achieve the first enantioselective synthesis of (+)-mitomycin K. Natural products with 6/5/5-fused ring skeletons are ubiquitous, and many of them possess interesting biological activities. Given the results disclosed above, our method holds great potential for the synthesis of such complex natural products in their innate enantiomeric forms.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** asymmetric synthesis · cyclization · mitomycin K · palladium · total synthesis

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[25] Direct comparison of our synthetic (+)-mitomycin K material with the natural compound by either optical rotation or HPLC analysis was prohibited by the unavailability of the latter as well as the lack of such data in the literature.

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# Communications

## Total Synthesis

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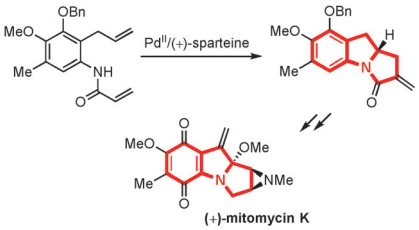


**Finally enantioselective**: Decades after its initial isolation, the first enantioselective synthesis of mitomycin K has been enabled by an asymmetric palladium-catalyzed oxidative tandem cyclization that quickly forged the ring skeleton with high enantioselectivity. Subsequent multistep manipulations provided (+)-mitomycin K with 97% *ee*.